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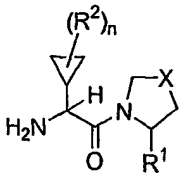
(54) Title: NEW DIPEPTIDYL PEPTIDASE IN INHIBITORS; PROCESS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract: The present invention relates to new dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula (I), and their analogs, isomers, pharmaceutical compositions and therapeutic uses, methods of making the same.

NEW DIPEPTIDYL PEPTIDASE IV INHIBITORS; PROCESS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

This application claims priority to Indian Provisional Application **1271/MUM/2003** filed on **December 15, 2003**, US Provisional Application **60/532,597** filed on **December 23, 2003** and Indian Provisional Application **17/MUM/2004** filed **January 07, 2004.** All of the above applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to new dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula (I), their analogs, tautomers, enantiomers, diastereomers, regioisomers, stereoisomers, polymorphs, pharmaceutically acceptable salts, N-oxides, pharmaceutically acceptable solvates and the pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Diabetes mellitus refers to a chronic metabolic disorder in which utilization of carbohydrates is impaired and that of lipid and proteins are enhanced. It is cause by an absolute or relative deficiency of insulin (the hormone which regulates the body's glucose utilization) and is characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test.

Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Patients with diabetes mellitus are at increased risk of macrovasuclar and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therapeutic control of

glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

Generally, there are two recognized forms of diabetes, known as type 1 and type 2. In type 1 diabetes, also known as insulin-dependent diabetes mellitus or "IDDM", patients produce little or no insulin. In type 2 diabetes, also known as non-insulin dependent diabetes mellitus or "NIDDM", patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects. NIDDM patients with elevated plasma insulin levels, however, often exhibit a developed resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin–sensitive tissues, including: muscle, liver and adipose tissues. Thus, the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance. Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor-binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue. In addition, insulin resistance results in insufficient glucose production and secretion in the liver.

Diabetes mellitus often develops in certain "at risk" populations. One such population is individuals with impaired glucose tolerance (IGT). The ordinary meaning of impaired glucose tolerance is a condition intermediate between normal glucose tolerance and NIDDM. IGT may be diagnosed by a test procedure that assesses an affected person's postprandial glucose response. In this test, a measured amount of glucose is given to the patient and blood glucose levels are measured at regular intervals. These intervals occur every half hour for the first two hours and every hour thereafter. In a "normal" or non-IGT individual, glucose levels rise during the first two hours to a level less than 140 mg/dl and then drop rapidly. In an individual with IGT, the blood glucose levels are higher and the drop-off level occurs at a slower rate. A high percentage of the IGT population is known to progress to NIDDM.

Insulin resistance is an abnormality of glucose disposal in tissues and organs, which can be measured by various tests, for example, the euglycemic glucose clamp test, the intravenous glucose tolerance test, or by measuring the fasting insulin level. It is well known that there is an excellent correlation between the height of the fasting insulin level and the degree of insulin resistance. Therefore, one could use elevated

fasting insulin levels as a surrogate marker for insulin resistance for the purpose of identifying which NGT individuals have insulin resistance.

U.S. Patent No. 5,702,012 discloses that a certain patient population that tests normal according to the fasting and two hour postprandial plasma glucose tests (i.e. normal glucose tolerance population) but exhibit insulin resistance using different tests, may progresses to NIDDM. This population is designated as having non-IGT (NIGT) or insulin resistant NIGT (IRNIGT). The reference further discloses that this population can be treated with thiazolidinedione class of compounds.

It is important to distinguish between those individuals whose tests show normal glucose tolerance and who are not insulin resistant on the one hand, and those who exhibit normal glucose tolerance with a certain degree of insulin resistance on the other hand.

The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories may dramatically improve the diabetic condition, compliance with this treatment is very poor because of sedentary lifestyles and excess food consumption. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β-cells to secrete more insulin, and/or by injection of insulin when sulphonylureas or meglitinide becomes ineffective, can results in insulin concentrations high enough to stimulate the very insulin-resistance tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide). In addition, the even higher plasma insulin levels may result in increased insulin resistance. The biguanide class of compounds can increase insulin sensitivity resulting in some correction of hyperglycemia. However, two biguanides, phenformin and metformin, can also induce lactic acidosis and nausea/diarrhea. Metformin, which has fewer side effects than phenformin, is often prescribed for the treatment of type 2 diabetes.

More recently, the glitazone class of compounds (i.e. 5-benzylthiazolidine-2,4-diones) have been used to ameliorate many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue resulting in partial or complete correction of the elevated plasma glucose levels without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the

PPAR-gamma subtype. This PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the PPAR agonists, such as troglitazone.

Dipeptidyl peptidase-IV ("DPP-IV") has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones glucagons-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms and removal of their two N-terminal amino acids will inactivate them. DPP-IV, a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, specifically removes the two N-terminal amino acids from proteins such as GIP and GLP-1 which have proline or alanine in position 2. Although the physiological role of DPP-IV has not been completely established, it is believed to play an important role in at least impaired fasting glucose (IFG) and diabetes.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, which results in (1) higher plasma concentrations of these hormones; (2) increased insulin secretion; and (3) improved glucose tolerance. Thus, such DPP-IV inhibitors have been proposed for the treatment of patients with type II diabetes, a disease characterized by decreased glucose tolerance. In addition, since the body produces these hormones only when food is consumed, DPP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DPP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is dangerous side effect associated with the use of insulin secretagoguese.

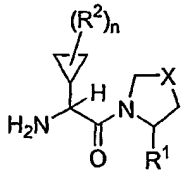
Currently there are a few compounds under review in advanced stages of human clinical trials that have been shown to inhibit DPP-IV. For example, such compounds have been disclosed in U.S. Patent No. 6,124,305, WO 98/19998, WO 03002530, WO 02083109, WO 00/34241, and WO 99138501, and, for example, Novartis "NVP-DPP-728", Probiodrug "P32/98", and Novartis "NVP-LAF-237".

Although the above DPP-IV inhibitors have been described in the literature, all have limitations relating to their potency, stability, selectivity and/or toxicity. Therefore, there still exists a need for novel DPP-IV inhibitors, which are therapeutically useful in the treatment of medical conditions mediated by DPP-IV inhibition.

SUMMARY OF THE INVENTION

The present invention relates to new Dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula (I), their analogs, their tautomers, their enantiomers, their diastereomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their N-oxides, their pharmaceutically acceptable solvates and the pharmaceutical compositions containing them.

The new compounds are of general formula (I)



(I)

wherein:

X is selected from $-S(O)_m$, $-CH_2-$, CHF, and $-CF_2$;

m is 0, 1 or 2;

n is 0, 1 , 2, 3 or 4;

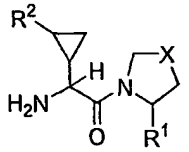
R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said of isosteres of carboxylic acids are selected from the group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, $-COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, $-NR^3COR^4$,NR^3COOR^4, $NR^3S(O)_mR^4$, $-S(O)_mNR^3R^4$, $-OCONR^3R^4$,- OR^3 ,$-R^3$,$-SR^3$.

R^3 and R^4 may be same or different and are independently selected from the group consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen,

substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

The present invention also includes compounds of the general formula (II)



(II)

wherein:

X is selected from $-S(O)_m$, $-CH_2-$, CHF, and $-CF_2$;

m is 0, 1 or 2;

R^1 is selected from hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said isosteres of carboxylic acids are selected from the group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, $-COOR^3$, $-CH_2OR^3$, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, $-NR^3COR^4$,NR^3COOR^4, $NR^3S(O)_mR^4$, $-S(O)_mNR^3R^4$, $-OCONR^3R^4$,$-OR^3$,$-R^3$,$-SR^3$.

R^3 and R^4 may be same or different and are independently selected from the group consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

Further preferred is the compound of general formula (II)

Further preferred is a compound of general formula (II), wherein R^1 is Hydrogen.

Further preferred is a compound of general formula (II), wherein R^1 is -CN.

Further preferred is a compound of general formula (II), wherein R^1 is $-CONH_2$.

Further preferred is a compound of general formula (II), wherein X is selected from $-CH_2-$,–CHF- and $-S(O)_m-$;wherein m is 0.

Further preferred is a compound of general formula (II), wherein R^2 is chosen from the group consisting of CN, COR^3, $COOR^3$, $-CH_2OR^3$ and $CONR^3R^4$.

Further preferred is a compound of general formula (II), wherein R^3 is hydrogen.

Further preferred is a compound of general formula (II), wherein R^3 is Methyl

Further preferred is a compound of general formula (II), wherein R^3 is Pyrrolidin-1yl

Further preferred is a compound of general formula (II), wherein R^3 is 4-Nitro phenyl

Further preferred is a compound of general formula (II), wherein R^3 is 4-Cyano phenyl

Further preferred is a compound of general formula (II), wherein R^4 is methyl

Further preferred is a compound of general formula (II), wherein R^4 is ethyl

Further preferred is a compound of general formula (II), wherein R^4 is isopropyl

Further preferred is a compound of general formula (II), wherein R^4 is n-hexyl.

Further preferred is a compound of general formula (II), wherein R^4 n-butyl.

Further preferred is a compound of general formula (II), wherein R^4 is 4-fluro phenyl

Some of the representative compounds according to the present invention are specified below but should not construed to be limited thereto:

1. Methyl(1*RS*,2*RS*)-2-{(1*RS*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate
2. Methyl (1*S*, 2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} cyclopropane-1-carboxylate trifluoroacetate
3. Methyl (1*R*, 2*R*)-2-{(1*R*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} cyclopropane-1-carboxylate trifluoroacetate
4. 1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-cyanocyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate
5. 1-{(2*S*)-amino-2-[(1*S*, 2*S*)-2-methylcarbamoylcyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide trifluoroacetate
6. 1-{2(*S*)-2-Amino-2-[(1S,2S)-2-methylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate
7. 1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile hydrochloride.
8. 1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-methylcarbamoylcyclopropyl]acetyl} pyrrolidine-2(*S*)-carbonitrile hydrochloride
9. 1-{(2S)-2-Amino-2-[(1S,2S)-2-ethylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2S)-carbonitrile trifluoroacetate
10. 1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-isopropylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate
11. 1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-isopropylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate
12. 1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-butylcarbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile trifluoroacetate
13. 1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-hexylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(*S*)-carbonitrile trifluoroacetate

14. 1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-azolanylcarbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile trifluoroacetate

15. 1-{2-(2*S*)-Amino-2-[(1*S*,2*S*)-2-(4-fluorophenylcarbamoyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate

16. 1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-nitrophenoxymethyl)cyclopropyl]ethanoyl} pyrrolidin-2-yl-(2*S*)-carbonitrile trifluoroacetate

17. 1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-nitrophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate

18. 1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)carbonitrile trifluoroacetate

19. 1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-cyanophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate

20. 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine trifluoroacetate

21. *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)1-amino-2-(pyrrolidin-1-yl)-2-oxoethyl]cyclopropane-1-carboxamide hydrochloride

22. *N*1-Methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(3*S*)-3-fluoropyrrolidin-1-yl]-2-oxoethyl}-cyclopropane-1-carboxamide hydrochloride

23. Methyl(1*RS*,2*RS*)-2-((1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl)cyclo-propane-1-carboxylate hydrochloride

24. *N*1-Methyl-(1*RS*,2*RS*)-2-[(1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl] cyclopropane-1-carboxamide hydrochloride

25. *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cyclo-propane-1-carboxamide hydrochloride

26. *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(4-(4*S*)-cyano-1,3-thiazolan-3-yl)ethyl] -cyclopropane-1-carboxamide trifluoroacetate

27. *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-ethoxycarbonylamino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxaamide

28. *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-acetoxyethoxycarbonylamino-2-[(2*S*)-2-cyanopyrrolin-1-yl]-2-oxoethyl}cyclopropane-1-carboxaamide

29. *N*1-methyl-(1S,2S)-2-{(1S)-1-[(2S)pyrrolidin-2-ylcarboxamido]-2-[(2S)-2-cyano pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide trifluoroacetate;
and pharmaceutically acceptable salts of the preceding compounds

A further aspect of the present invention is also the corresponding pharmaceutically acceptable salts such as trifluoroacetate salt, hydrochloride salt etc. but not to be limited thereto for the above five compounds.

A further aspect of the present invention is a pharmaceutical composition useful in the treatment and/or prophylaxis of diseases, which are associated with DPP-IV, the composition comprising, as an active ingredient, a compound according to Formula I thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention is a method for the treatment and/or prophylaxis of diseases which are associated with DPP-IV, selected from the group consisting of diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, ulcerative colitis, Crohn's disease, obesity, and metabolic syndrome, which method comprises administering to a host suffering therefrom a therapeutically effective amount of a compound according to Formula I.

A further aspect of the present invention is a method of treating insulin resistant non-impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Formula I.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of a condition that may be regulated or normalized via inhibition of DPP-IV.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of metabolic disorders.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for blood glucose lowering.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of Type II diabetes.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of impaired glucose tolerance (IGT).

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of impaired fasting glucose (IFG).

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the prevention of hyperglycemia.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of impaired glucose tolerance (IGT) to Type II diabetes.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for increasing the number and/or the size of beta cells in a subject.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of beta cell degeneration, in particular apoptosis of beta cells.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of disorders of food intake.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of obesity.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for appetite regulation or induction of satiety.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of dyslipidemia.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of functional dyspepsia, in particular irritable bowel syndrome.

DETAILED DESCRIPTION

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like .

The term "alkenyl " refers to aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term " alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, butnyl and the like.

The term "alkoxy" denotes alkyl group as defined above attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are – OCH_3, $-OC_2H_5$ and the like.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups e.g. sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms directly attached to alkyl group which are then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, and the like.

The term "cycloalkenyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with at least one carbon- carbon double bond such as cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl and the like.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, for example, $-CH_2C_6H_5$, $-C_2H_5C_6H_5$ and the like.

The term "heterocyclic ring" refers to a stable 3 to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl , oxadiazolyl , chromanyl, isochromanyl and the like. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroaryl" refers to heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to heteroaryl ring radical as defined above directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocyclic ring radical as defined above. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical as defined above directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

The term isosteres of carboxylic acids include but are not limited to SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides.

The term amide includes but is not limited to $CONR^3R^4$ where R^3 and R^4 are independently selected for each occurrence and are as previously defined.

The term ester includes but is not limited to $COOR^3$ where R^3 is independently selected for each occurrence and is as previously described except R^3 cannot be hydrogen.

The substituents in the 'substituted alkyl', 'substituted alkoxy', 'substituted alkenyl', 'substituted alkynyl', 'substituted cycloalkyl', 'substituted cycloalkylalkyl', 'substituted cyclocalkenyl', 'substituted arylalkyl', 'substituted aryl', 'substituted heterocyclic ring', 'substituted heteroaryl ring', 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring', 'substituted amino', and 'substituted carboxylic acid derivative' may be the same or different which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio(=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclylalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclylalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring,

The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (II) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (III) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means

causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by local or by systemic administration of the active ingredient to the host.

The term "prophylaxis" involves the administration of a compound of the invention prior to the clinical appearances of the disease or prior to the induction of the disease.

The term "subject" or "a patient" or "a host" as used herein refers to mammalian animals, preferably human.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; salts of organic bases such as N,N'-diacetylethylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, thiamine, and the like; chiral bases like alkylphenylamine, glycinol, phenyl glycinol and the like, salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, serine, and the like; quaternary ammonium salts of the compounds of invention with alkyl halides, alkyl sulphates like MeI, $(Me)_2SO_4$ and the like, non-natural amino acids such as D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate, which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates such as trifluroacetate, tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy, 19th Supp. Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or

coloring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of the invention, which inhibits the enzymatic activity of DPP-IV, dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers, such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional tabletting techniques may contain: 1 Core: Active compound (as free compound or salt thereof) 250 mg Colloidal silicon dioxide (Aerosil®) 1.5 mg Cellulose, microcryst. (Avicel®) 70 mg Modified cellulose gum (Ac-Di-Sol®) 7.5 mg Magnesium stearate Ad. Coating: HPMC approx. 9 mg *Mywacett 9-40 T approx. 0.9 mg *Acylated monoglyceride used as plasticizer for film coating.

Where the term compound of Formula I is used, it is understood that this also encompasses subgeneric formula II.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of the various diseases as mentioned above, e.g., Type II diabetes, IGT, IFG, obesity, appetite regulation or as a blood glucose lowering agent, and especially Type II diabetes. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day may be used. More preferably, the dosage is about 0.5 mg to about 250 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

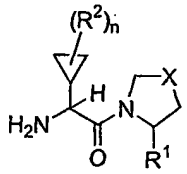
Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

The invention also encompasses prodrugs of a compound of the invention, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compound of the invention, which are readily convertible in vivo into a compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of a compound of the invention.

The present invention discloses a process for the preparation of compounds of general formula (I).



(I)

wherein:

X is selected from $-S(O)_m$, $-CH_2-$, CHF, and $-CF_2$;

m is 0, 1 or 2;

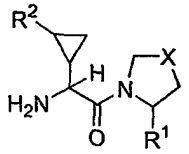
n is 0, 1 , 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said of isosteres of carboxylic acids are selected from the group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, $-COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, $-NR^3COR^4$,NR^3COOR^4, $NR^3S(O)_mR^4$, $-S(O)_mNR^3R^4$, $-OCONR^3R^4$,$-OR^3$,$-R^3$,$-SR^3$.

R^3 and R^4 may be same or different and are independently selected from the group consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

The present invention also includes compounds of the general formula (II) disclosed wherein Formula (II) has the structure;



(II)

wherein:

X is selected from $-S(O)_m$, $-CH_2-$, CHF, and $-CF_2$;

m is 0, 1 or 2;

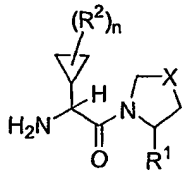
R^1 is selected from hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said isosteres of carboxylic acids are selected from the group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, $-COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, $-NR^3COR^4$,NR^3COOR^4, $NR^3S(O)_mR^4$, $-S(O)_mNR^3R^4$, $-OCONR^3R^4$,- OR^3 ,$-R^3$,$-SR^3$.

wherein R^3 and R^4 may be same or different and are independently selected from the group consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

The compounds according to the invention may be prepared by the following processes. The symbols X, $R^1$and R^2 when used in the formulae below are to be understood to present those groups described above in relation to formula (I) unless otherwise indicated

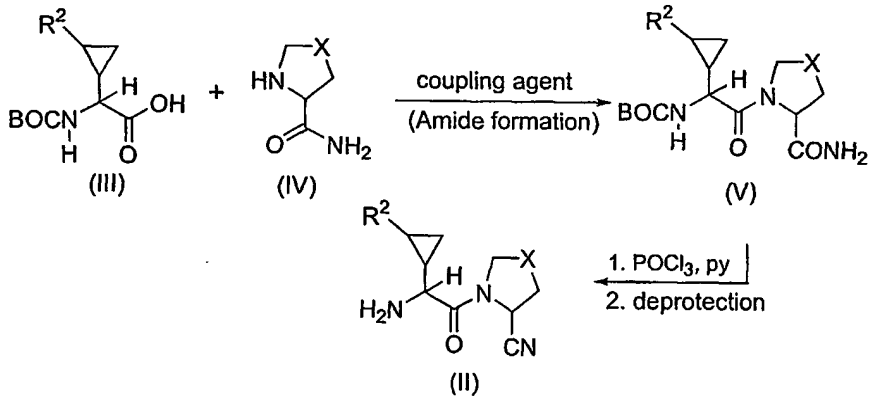
The present invention discloses a process for the preparation of compounds of general formula (I).



(I)

In one embodiment the desired compounds of the formula (I) as described in the general description can be synthesized as described in the general synthetic scheme I.

Scheme 1

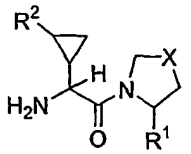


which comprises coupling a compound of general formula (III) with a compound of the general formula (IVA) under standard peptide coupling conditions, for example, using EDC, HOBt, and a base, generally diisopropylethylamine, in a solvent such as DMF or methylene chloride for about 3 to about 48 hours at ambient temperature followed by de-protection using common methods known in the art to give the compounds of general formula (I).

It is also understood that the compounds of general formula (III) used for the coupling reaction may be further modified before formation of the compounds of general formula (I), for example, by manipulation of substituents on R^2. These manipulations

may include, but are not limited to, substitution, reduction, oxidation, alkylation, acylation, and hydrolysis reaction which are commonly known to those skilled in the art.

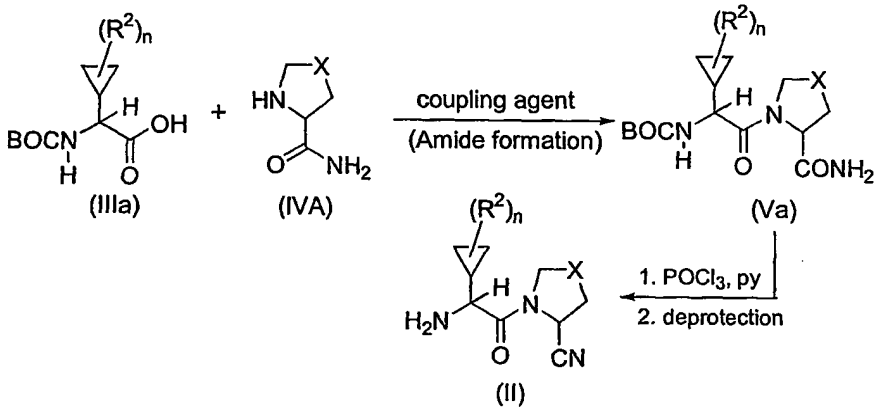
Further, the preferred compounds of the general formula (II)



(II)

wherein all groups are as previously described; may be prepared by a process as described in the scheme 2

Scheme 2

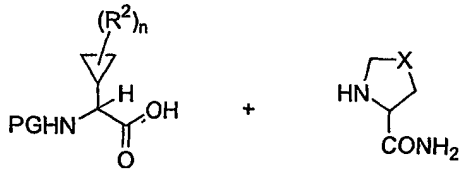


which comprises coupling a compound of general formula (IIIa) with a compound of the general formula (IVA) under standard peptide coupling conditions, for example, using EDC, HOBt, and a base, generally diisopropylethylamine, in a solvent such as DMF or methylene chloride for about 3 to about 48 hours at ambient temperature to provide intermediate (Va) .This is then treated with dehydrating agent such as $POCl_3$ /Pyridine followed by deprotection using common methods known in the art to give the preferred compounds of the formula (II) wherein R^1 is nitrile.

It is also understood that the compounds of general formula (IIIa) and/or (Va) as described in Scheme 2 may be further modified before formation of the preferred compound of the formula (I) wherein R^1 is nitrile, for example, by manipulation of

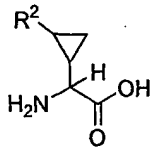
substituents on R^2. These manipulations may include, but are not limited to, substitution, reduction, oxidation, alkylation, acylation, and hydrolysis reaction which are commonly known to those skilled in the art.

The compounds of general formula (III) and formula (IV) can be prepared using a variety of methods known in the literature and known to those skilled in the art.



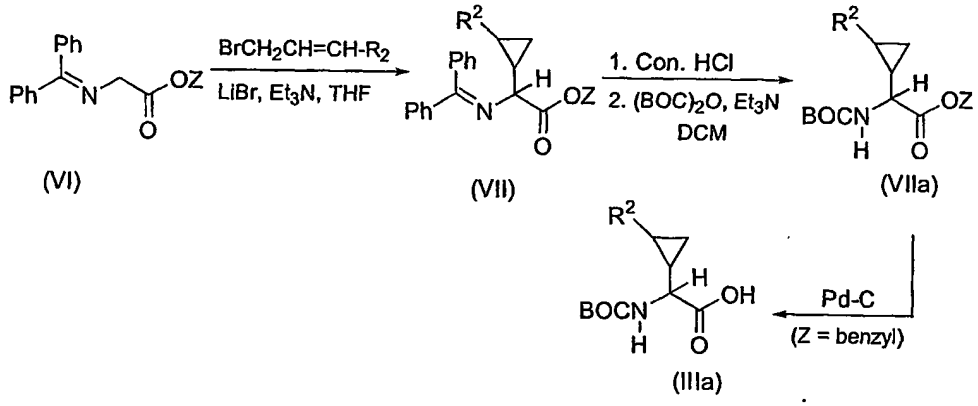
(III) (IV)

The compounds of the formula (III.a) can be prepared in accordance to the Scheme 3:



(IIIa)

Scheme 3



wherein, Z is alkyl such as methyl, ethyl, t-butyl; arylalkyl such as benzyl group.

Synthesis of compound VI can be found in the following reference: O'Donnell et al., *J. Org. Chem.*, **1982**, *47*, 2663-2666.

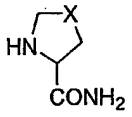
R^2 is selected from groups consisting of cyano, formyl, acetyl, substituted or unsubstituted amide, $-COOR^3$, COR^3, $.CONR^3R^4$, and nitro. Similarly compound VII with different stereochemistry can be synthesized as given above or in the following references: Chavan et al., *J. Org. Chem.*, **2003**, *68*, 6817-6819, Chavan et al.,

Tetrahedron Letters, **1996,** *37,* 2857-2858, Kurokowa et al., *Tetrahedron Letters,* **1985,** *26,* 83-84, Shimamoto et al., *Tetrahedron Letters,* **1989,** *29,* 3803-3804, Yamanoi et al., *Tetrahedron Letters,* **1988,** *29,* 1181-1184 .

R^3 and R^4 may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

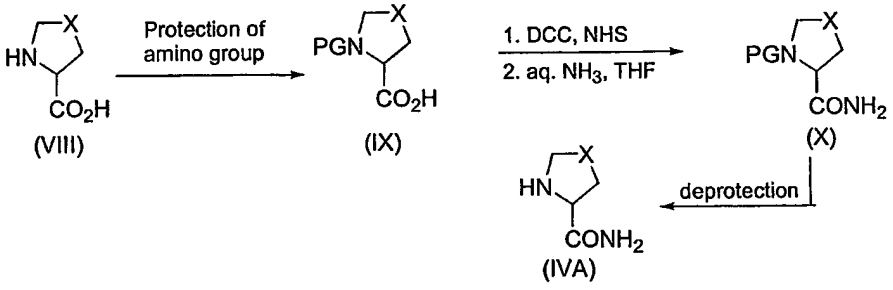
Further R^2 group in the compound (VII) may be modified to give before converting it to Compound (IIIa). These modifications may include, but are not limited to, substitution, reduction, oxidation, alkylation, acylation and hydrolysis reaction which are commonly known to those skilled in the art.

In specific, the compounds of formula (IVA) can be prepared in accord to the Scheme 4



(IVA)

Scheme 4



wherein,

Pg represents a suitable nitrogen protecting group such as BOC, CBZ, and FMOC.

X is selected from -S (O) m, -CH_2-, CHF, and -CF_2;

wherein, m is 0, 1 or 2.

One of the possible routes for synthesis of compound of formula (IVA) shown in scheme 4 involves treatment of a carbamate derivative (VIII) with N-hydroxy succinimide (NHS) and DCC or other suitable coupling agent in a solvent such as dichloromethane for about 1 to about 24 hours. The resulting product (IX) is then treated with a base, for example, aqueous ammonium hydroxide in a solvent such as dioxane. Deprotection of compound (X) using common methods known in the art gives the desired compound (IVA). Further the carbamate derivative (VIII) is commercially available or may be conveniently prepared by methods in the literature or known to those skilled in the art.

The compounds in accordance to the invention are isolated and purified in a manner known per se, for example, by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, for example, in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (for example, ethanol or isopropanol), which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecepitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn, can be converted into salts.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula (I) are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like. The aromatic solvents which may be employed may be selected from benzene and toluene. The alcoholic solvents which may be employed may be selected from methanol, ethanol, n-propanol, iso propanol, tert-butanol and the like. The aprotic solvents which may be

employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, isopropanol, water or their combinations, or column chromatography using alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions, for example, using different solvents commonly used or their mixtures for recrystallization, crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention provides new organic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diastereomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate N-oxides and their pharmaceutically acceptable solvates.

The present invention also provides pharmaceutical compositions, containing compounds of general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diastereomers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

It will be appreciated that some of the compounds of general formula (I) defined above according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of general formula (I) can give rise to stereoisomers and in each case the invention is to be understood to extend to all such stereoisomers, including

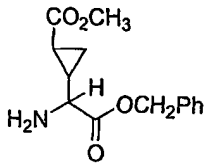
enantiomers and diastereomers and their mixtures, including racemic mixtures. The invention may also contain E & Z geometrical isomers wherever possible in the compounds of general formula (I) which includes the single isomer or mixture of both the isomers

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Intermediates

Intermediate 1

Benzyl (2*SR*)-2-amino-2-[(1*SR*, 2*SR*)-2-methyloxycarbonylcyclopropyl] acetate



Step 1: Benzyl *N*-(diphenylmethylene) glycinate: This intermediate is commercially available. Alternatively it can be prepared from diphenylimine and benzyl glycinate by a literature procedure (O'Donnel, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663-2666).

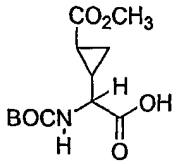
Step 2: Benzyl (2*SR*)-2-(diphenylmethyleneamino-2-[(1*SR*,2*SR*)-2-methyloxycarbonyl-cyclopropyl]acetate hydrochloride: To a solution of benzyl *N*-(diphenylmethylene)-glycinate (50.0 g, 151.79 mmol), methyl-4-bromocrotonate (34.0 g, 189.74 mmol) and lithium bromide (19.8 g, 189.74 mmol) in dry THF (900 ml) was added triethylamine (26.4 ml, 189.74 mmol) in dry THF (100 ml) over a period of 45 min. The reaction mixture was stirred for 20 h at room temperature. The mixture was diluted with cold water (500 ml) and then extracted with ethyl acetate (4 x 500 ml). The combined organic extracts were acidified with 10*N* hydrochloric acid (40 ml) and the mixture was stirred for 30 min at room temperature. The amine hydrochloride precipitated out was collected by filtration to give 31 g (68 %) of the product as a white solid; Mp: 208 °C, IR (KBr) 3423, 2953, 2627, 2464, 1756, 1717, 1499, 1398, 1367, 1297, 1220, 1037, 753 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ

1.11-1.17 (m, 1H), 1.21-1.27 (m, 1H), 1.66-1.71 (m, 1H), 2.00-2.06 (m, 1H), 3.61 (s, 3H), 3.74-3.77 (br d, J = 9.3 Hz, 1H), 5.22-5.26 (d, J = 12.3 Hz, 1H), 5.27-5.31 (d, J = 12.3 Hz, 1H), 7.38-7.41 (m, 5H), 8.78 (br s, 3H).

Step 3: Benzyl (2*SR*)-2-(diphenylmethyleneamino-2-[(1*SR*,2*SR*)-2-methyloxycarbonyl-cyclopropyl]acetate: The amine hydrochloride (30.0 g, 100.07 mmol) from Step 2 was basified to pH 8.0 using 2*N* NaOH solution. The aqueous solution was extracted with ethyl acetate (3 x 300 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give to 24.0 g (91 %) of the product as a viscous liquid; IR (neat) 3362, 3032, 2953, 1731, 1455, 1278, 1210, 1175, 1024, 930, 751, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (m, 1H), 1.19 (m, 1H), 1.70 (m, 2H), 2.04 (br s, 2H), 3.65 (s, 3H), 3.68 (m, 1H), 5.20 (m, 2H) 7.29-7.4 (m, 5H).

Intermediate 2

(2*SR*)-2-(*tert*-Butyloxycarbonylamino)-2-[(1*SR*,2*SR*)-2-methyloxycarbonylcyclopropyl]acetic acid



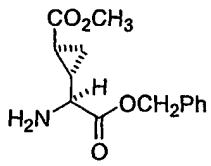
Step 1: Benzyl (2*SR*)-2-(*tert*-Butoxycarbonylamino-2-[(1*SR*,2*SR*)-2-methyloxycarbonylcyclopropyl]acetate: Di-*tert*-butyl dicarbonate (7.3 g, 33.84 mmol) was added to a solution of Intermediate 1 (8.1 g, 30.76 mmol) in dichloromethane (200 ml) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using 10 % ethyl acetate in petroleum ether as eluent to afford 9.1 g (81%) of the product as a viscous oil; IR (neat) 3367, 3033, 2978, 1715, 1722, 1514, 1344, 1248, 1168, 1024, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10-1.08 (m, 1H), 1.19-1.22 (m, 1H), 1.43 (s, 9H), 1.71-1.76 (m, 2H), 3.64 (s, 3H), 4.06-4.13 (m, 1H), 5.10-5.27 (m, 2H), 7.34-7.38 (m, 5H).

Step 2: To a solution of Step 1 intermediate (9.1 g, 25.04 mmol) in methanol (200 ml) was added 5 % Pd-C (2.0 g) and the mixture was stirred under hydrogen atmosphere

for 15 h. The reaction mixture was filtered to remove the catalyst and the solvent was evaporated under reduced pressure to give 6.25 g (92 %) of the product as a viscous oil; IR (neat): 3368, 3071, 2653, 1747, 1724, 1651, 1457, 1406, 1356, 1254, 1181, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08-1.14 (m, 1H), 1.26-1.33 (m, 1H), 1.45 (s, 9H), 1.77-1.79 (m, 2H), 3.68 (s, 3H), 3.97 (br s, 1H), 5.14 (br d, J = 6.9 Hz, 1H), 6.80 (br s, 1H).

Intermediate 3

Benzyl (2*S*)-2-amino-2-[(1*S*,2*S*)-2-methyloxycarbonylcyclopropyl]acetate



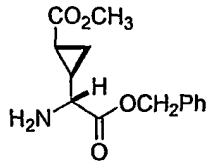
A mixture of Intermediate 1 (10 g, 37.98 mmol) and dibenzoyl-D-tartaric acid (13.61 g, 37.98 mmol) in acetonitrile (50 ml) was heated to reflux. A minimum amount of methanol was added to the refluxing mixture to result a clear solution. The hot solution was diluted with acetonitrile (250 ml) and further allowed to cool to room temperature over a period of 30 min. The mixture was further stirred at RT to result a white precipitate. The precipitated diastereomeric salt was collected by filtration. The free amine was regenerated by basification of the salt using aqueous sodium hydroxide. The aqueous solution was extracted with dichloromethane (3 x 100 ml) and the combined organic extracts were washed with brine (50 ml) and dried over anhydrous potassium carbonate. The solvent was evaporated under reduced pressure to yield 2.5 g of the product in >98 % ee as determined by chiral HPLC; $[\alpha]_D^{20}$ = + 47.23 (c = 0.81, $CHCl_3$); IR (neat) 3383, 2952, 1729, 1607, 1498, 1454, 1277, 1208, 1171, 1027, 926, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.12 (m, 1H), 1.19-1.24 (m, 1H), 1.16-1.66 (m, 1H), 1.68-1.76 (m, 1H), 3.16 (d, J = 7.2 Hz, 1H), 3.65 (s, 3H), 5.14 (d, J = 12 Hz, 1H), 5.20 (d, J = 12.3 Hz, 1H), 7.25-7.28 (m, 5H).

The absolute stereochemistry of the product was assigned by its conversion to methyl 2-*tert*-butoxycarbonylamino(methyloxycarbonyl)methyl-1-cyclopropanecarboxylate

having known its relative and absolute stereochemistry; $[\alpha]_D$ = + 109.5 (c = 0.89, $CHCl_3$) Lit. $[\alpha]_D$ = + 108.6 (c = 0.88, $CHCl_3$), *J. Org. Chem.* **2003**, *68*, 6817.

Intermediate 4

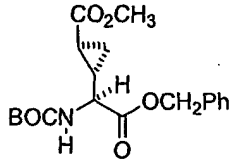
Benzyl (2*R*)-2-amino-2-[(1*R*,2*R*)-2-methyloxycarbonylcyclopropyl]acetate



This intermediate was prepared by the resolution of Intermediate 1 using dibenzoyl-L-tartaric acid as described for Intermediate 2.; $[\alpha]_D^{20}$ = - 42.86 (c = 0.74, $CHCl_3$); IR (neat) 3383, 2952, 1729, 1607, 1498, 1454, 1277, 1208, 1171, 1027, 926, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.12 (m, 1H), 1.18-1.24 (m, 1H), 1.64-1.66 (m, 1H), 1.68-1.74 (m, 1H), 3.16 (d, *J* = 7.2 Hz, 1H), 3.65 (s, 3H), 5.14 (d, *J* = 12.6 Hz, 1H), 5.20 (d, *J* = 12.6 Hz, 1H), 7.26-7.29 (m, 5H).

Intermediate 5

Benzyl (2*S*)-2-(*tert*-butyloxycarbonylamino)-2-[(1*S*,2*S*)-2-methyloxycarbonylcyclo-propyl]acetate



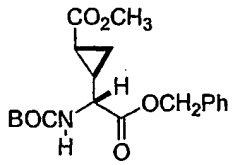
A solution of di-*tert*-butyl dicarbonate (0.20 g, 0.919 mmol) in dichloromethane (5 ml) was added to a solution of Intermediate 3 (0.22 g, 0.836 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column

chromatography using 10 % ethyl acetate in petroleum ether as eluent to afford 0.32 g of the product as a viscous oil; $[\alpha]_D$ = + 45.14 (c = 0.65, CH_3OH); IR (neat) 3362, 2928, 1713, 1509, 1367, 1208, 1164, 1047, 1021, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02-1.08 (m, 1H), 1.19-1.26 (m, 1H), 1.43 (s, 9H), 1.68-1.76 (m, 2H), 3.65

(s, 3H), 4.04 (br t, 1H), 5.10 (br s, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.26 (d, J = 12.3 Hz, 1H), 7.15-7.21 (m, 5H).

Intermediate 6

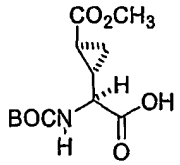
Benzyl (2*R*)-2-(*tert*-butyloxycarbonylamino)-2-[(1*R*,2*R*)-2-methyloxycarbonylcyclo-propyl]acetate



This intermediate was prepared from Intermediate 4 (0.20 g, 0.76 mmol) and di-*tert*-butyl dicarbonate (0.18 g, 0.83 mmol) in dichloromethane (10 ml) as described for Intermediate 5 to give 0.260 g (94 %) of the product as a viscous liquid; $[\alpha]_D$ = - 44.33 (c = 0.623, CH_3OH); IR (neat): 3361, 2929, 1710, 1512, 1365, 1212, 1162, 1044, 1025, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01-1.08 (m, 1H), 1.19-1.25 (m, 1H), 1.43 (s, 9H), 1.71-1.76 (m, 2H), 3.64 (s, 3H), 4.04 (br t, 1H), 5.09 (br s, 1H), 5.13 (d, J = 12.6 Hz, 1H), 5.23 (d, J = 12.6 Hz, 1H), 7.26-7.28 (m, 5H).

Intermediate 7

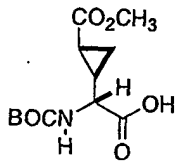
Benzyl (2*S*)-2-(*tert*-butyloxycarbonylamino)-2-[(1*S*,2*S*)-2-methyloxycarbonylcyclo-propyl]acetic acid



To a solution of Intermediate 5 (0.30 g, 0.825 mmol) in methanol (20 ml) was added 5 % Pd-C (0.125 g) and the mixture was stirred under hydrogen atmosphere for 15 h. The reaction mixture was further filtered to remove the catalyst and the solvent was evaporated under reduced pressure to give 0.220 g (98 %) of the product as a viscous oil; $[\alpha]_D$ = + 107.36 (c = 0.61, CH_3OH); IR (neat): 3355, 2979, 1713, 1516, 1452, 1395, 1368, 1171, 1050, 1023, 933 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-0.88 (m, 1H), 1.01-1.20 (br m, 1H), 1.21-1.35 (br m, 1H) 1.43, 1.45 (s, 9H), 1.68-1.88 (m, 1H), 3.68 (s, 3H), 3.88-4.08 (br s, 1H), 5.17 (br s, 1H), 6.75 (br s, 1H).

Intermediate 8

Benzyl (2*R*)-2-(*tert*-butoxycarbonylamino)-2-[(1*R*,2*R*)-2-methyloxycarbonylcyclopropyl]acetic acid

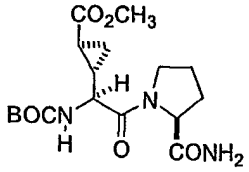


This compound was prepared from Intermediate 6 (0.28 g, 0.77 mmol) using 5 % Pd/C (0.120 g) in methanol (20 ml) as described in Intermediate 7 to give 0.163 g (77 %) of the product as a viscous oil; $[\alpha]_D$ = - 94.31 (c = 0.3, CH_3OH); IR (neat): IR (neat): 3356, 2974, 1710, 1519, 1454, 1391, 1367, 1175, 1058, 1022, 936 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07-1.14 (m, 1H), 1.25-1.31 (br m, 1H), 1.45 (s, 9H), 1.57-1.80 (m, 2H), 3.68 (s, 3H), 3.96 (br s, 1H), 5.13 (br s, 1H), 6.72 (br s, 1H).

Intermediate 9

Methyl carbamoylpyrrolidin-1-yl] -2-oxoethyl}cyclopropane -1-carboxylate

(1*S*,2*S*)-2-{(1*S*)-1-(*tert*-butyloxycarbonylamino)-2-[(2*S*)-2-



Method A

To a stirred and cooled (0 °C) mixture of Intermediate 7 (10.0 g, 36.59 mmol) and 1-hydroxybenzotriazole (5.92 g, 43.91 mmol) in dichloromethane (200 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.41 g, 43.91 mmol) in portions and the mixture was stirred for 0.5 h at the same temperature to result a clear solution. L-prolinamide (5.00 g, 43.91 mmol) in dichloromethane (50 ml) was further added followed by addition of diisopropylethyl amine (6.6 g, 51.22 mmol). The mixture was stirred for 20 h at room temperature and diluted with dichloromethane (200 ml). The solution was washed with 1*N* HCl (100 ml), water (2 x 100 ml), brine (100 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 11.3 g (84 %) of the product as a white solid; mp 178-182 °C; IR (KBr) 3389, 3346, 3215, 2994, 1725, 1675, 1645, 1522, 1430, 1313, 1265,

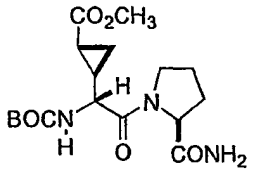
1165, 1090, 1025, 903, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (m, 1H), 1.23 (m, 1H), 1.42, 1.43 (s, 9H), 1.79 (m, 2H), 1.9-2.5 (m, 3H), 2.4 (m, 1H), 3.62 (m, 2H), 3.67 (s, 3H), 4.46 (m, 1H), 4.62 (dd, J = 7.8,3.0 Hz, 1H), 5.29 (br s, 1H), 5.32, 5.36 (s, 1H), 6.64 (br s, 1H).

Method B

To a stirred and cooled (0 °C) mixture of Intermediate 2 (6.84 g, 25 mmol) and 1-hydroxybenzotriazole (4.05 g, 30 mmol) in dichloromethane (150 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.75 g, 30 mmol) in portions and the mixture was stirred for 0.5 h at the same temperature to result a clear solution. L-prolinamide (3.42 g, 30.3 mmol) in dichloromethane (50 ml) was further added followed by addition of diisopropylethyl amine (6.46 g, 50 mmol). The mixture was stirred for 20 h at room temperature and diluted with dichloromethane (150 ml). The solution was washed with 1*N* HCl (100 ml), water (100 ml), brine (100 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 7.2 g (78 %) of the product as a 1:1 mixture of diastereomers. These diastereomers were separated by flash silica gel column chromatography using 3 % methanol in dichloromethane as eluent. The more polar isomer was identical in all respects with the product obtained by Method A.

Intermediate 10

Methyl (1*R*,2*R*)-2-{(1*R*)-1-(*tert*-butyloxycarbonylamino)-2-[(2*S*)-2-carbamoylpyrroli- din-1-yl] -2-oxoethyl}cyclopropane -1-carboxylate



Method A

To a stirred and cooled (0 °C) mixture of Intermediate 8 (10.0 g, 36.59 mmol) and 1-hydroxybenzotriazole (5.92 g, 43.91 mmol) in dichloromethane (200 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.41 g, 43.91mmol) in portions and the mixture was stirred for 0.5 h at the same temperature to result a clear solution. L-prolinamide (5.00 g, 43.91 mmol) in dichloromethane (50 ml) was further added followed by addition of diisopropylethyl amine (6.6 g, 51.22 mmol).

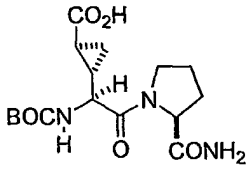
The mixture was stirred for 20 h at room temperature and diluted with dichloromethane (200 ml). The solution was washed with 1*N* HCl (100 ml), brine (100 ml) and dried (Na_2SO_4. The solvent was evaporated under reduced pressure to give 10.8 g (80 %) of the product as a white solid; the isolated from was characterized as the R,R,R-isomer after converting it to a compound of known relative and absolute stereochemistry; mp 75-80 °C; IR (KBr) 3413, 3344, 2980, 1729, 1695, 1645, 1521, 1440, 1368, 1281, 1254, 1172, 1050, 892, 638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (m, 1H), 1.26 (m, 1H), 1.41, 1.43 (s, 9H), 1.70 (m, 1H), 1.80 (m, 1H), 2.05 (m, 3H), 2.37 (m, 1H), 3.51 (m, 1H), 3.68 (s, 3H), 3.88 (m, 1H), 4.12 (t, J = 7.5 Hz, 1H), 4.59 (m, 1H), 5.25 (br s, 1H), 5.31 (m, 1H), 6.87 (br s, 1H).

Method B

The less polar diastereomer isolated from Intermediate 9, Method B was identical in all respects with that isolated from Intermediate 10, Method A

Intermediate 11

(1*S*,2*S*)-2-{(1*S*)-1-(*tert*-butyloxycarbonylamino)-2-[(2*S*)-2-carbamoylpyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylic acid

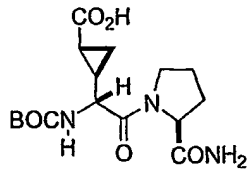


To a stirred solution of Intermediate 9 (500 mg, 1.35 mmol) in 20 % aqueous THF (50 ml) was added lithium hydroxide monohydrate (284 mg, 6.76 mmol) and the mixture was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the reaction mixture was diluted with water (100 ml). The basic aqueous solution was washed with ethyl acetate (2 x 100 ml) and then acidified to pH 2 with 1*N* HCl. The acidic aqueous solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 437 mg (91 %) of the product as a white solid; IR (KBr) 3414, 2980, 2927, 1700, 1642, 1450, 1252, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-1.02 (m, 1H), 1.20-1.36 (m, 2H), 1.42 (s, 9H), 1.60-1.66 (m, 1H), 1.73-1.82 (m, 1H), 1.90-2.18 (m, 2H), 2.30-2.40 (m, 1H),

3.65-3.70 (m, 2H), 4.60-4.73 (m, 2H), 5.43 (d, J = 7.5 Hz, 1H), 6.68 (br s, 1H), 7.24 (br s, 1H).

Intermediate 12

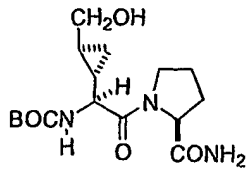
(1*R*,2*R*)-2-{(1*R*)-1-(*tert*-butoxycarbonylamino)-2-[(2*S*)-2-carbamoylpyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylic acid



This intermediate was prepared from Intermediate 10 (7.0 g, 18.94 mmol) as described in Intermediate 11 using lithium hydroxide monohydrate (3.1 g, 75.79 mmol) in 20 % aqueous THF (350 ml) to give 6.6 g (98 %) of the product as a white solid; IR (KBr) 3327, 2929, 2978, 1698, 1506, 1425, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.10 (m, 1H), 1.23-1.34 (m, 2H), 1.41, 1.43 (s, 9H), 1.62-1.72 (m, 1H), 1.79-1.89 (m, 1H), 2.00-2.18 (m, 2H), 2.30-2.36 (m, 1H), 3.50-3.54 (m, 2H), 3.80-4.00 (m, 1H), 4.57-4.59 (m, 1H), 5.70-5.79 (m, 1H), 5.98-6.08 (m, 1H), 6.90-7.02 (m, 1H).

Intermediate 13

(2*S*)-1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-hydroxymethylcyclopropyl]-ethanoyl}pyrrolidin-2-carboxamide



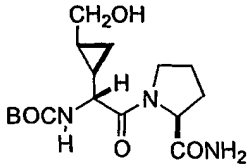
Ethyl chloroformate (913 mg, 8.44 mmol) was added to a stirred solution of Intermediate 11 (3.0 g, 8.44 mmol) and triethylamine (860 mg, 8.44 mmol) in dry THF (20 ml) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was filtered to remove triethylamine hydrochloride and the filtrate containing the

mixed anhydride was added drop wise to a stirred solution of $NaBH_4$ (957 mg, 25.32 mmol) in 20 % aqueous THF (40 ml) at 10 °C. The mixture was further stirred at the same temperature for 1 h and acidified to pH 4 with saturated NH_4Cl solution at 0 °C.

THF was evaporated under reduced pressure and the residue was diluted with water (50ml). The aqueous solution was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried ($NaSO_4$) and evaporated under reduced pressure to give a viscous residue. The residue was purified by silica gel column chromatography using 6 % methanol in dichloromethane to afford 1.6 g (56 %) of the product as a white solid; IR (KBr) 3423, 2979, 1684, 1638, 1448, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.42-0.49 (m, 1H), 0.59-0.65 (m, 1H), 1.09- 1.15 (m, 2H), 1.42 (s, 9H), 1.99-2.20 (m, 5H), 2.94 (dd, J = 8.7, 11.4 Hz, 1H), 3.71- 3.77 (m, 2H), 3.86 (dd, J = 4.2, 11.4 Hz, 1H), 4.5-4.54 (m, 1H), 4.6 (dd, J = 4.8, 7.2 Hz, 1H), 5.40 (d, J = 7.8 Hz, 1H), 5.9 (br s, 1H), 6.62 (br s, 1H).

Intermediate 14

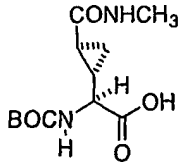
(2*S*)-1-{(2*R*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2hydroxymethylcyclopropyl] -ethanoyl}pyrrolidin-2-carboxamide



This compound was prepared from Intermediate 12 (1.0 g, 2.18 mmol) as described in Intermediate 13 using ethyl chloroformate (305 mg, 2.81mmol), triethylamine (284 mg, 2.81mmol) and $NaBH_4$ (0.320 g, 8.44 mmol) to give 664 mg (56 %) of the alcohol as a white solid; IR (KBr) 3406, 2979, 1674, 1642, 1522, 1444, 1251, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.51-0.57 (m, 1H), 0.62-0.68 (m, 1H), 1.10-1.18 (m, 2H), 1.40-1.42 (s, 9H), 1.98-2.13 (m, 3H), 2.18-2.30 (m, 1H), 2.48 (br s, 1H), 3.09-3.15 (m, 1H), 3.50-3.55 (m, 1H), 3.77-3.83 (m, 2H), 3.91-3.93 (m, 1H), 4.56 (d, J = 7.5 Hz, 1H), 5.68 (br s, 1H), 6.11 (br s, 1H), 7.12 (br s, 1H).

Intermediate 15

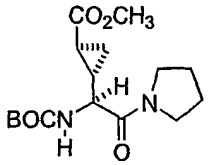
(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclopropyl] ethanoic acid



To a stirred solution of Intermediate 7 (2 gm, 7.31mmol) in THF (20.0 ml) was added 40 % aqueous methylamine (20.0 ml) and the solution were stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure and the residue obtained was diluted with water (25 ml), acidified with 1*N* HCl solution. The solution was extracted with dichloromethane (3 x 100 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was stirred in 1% EtOAc in pet. ether (50ml) and filtered to afford the pure compound as a white solid (1.64g ,80%). IR (KBr) 3383, 1698, 1639, 1252, 1164 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6) δ 0.78-0.82 (m, 1H), 0.85-0.91 (m, 1H), 1.37 (s, 9H), 1.42-1.45 (m, 1H), 1.48-1.52 (m, 1H), 2.55 (d, J = 4.2 Hz, 3H), 7.34 (d, J = 7.8 Hz, 1H), 7.94-7.95 (m, 1H), 12.6 (br s, 1H).

Intermediate 16

Methyl (1*S*,2*S*)-2-[(1*S*)-1-(*tert*-Butoxycarbonyl)amino-2-(1-pyrrolidin)-2-oxoethyl] cyclopropane-1-carboxylate

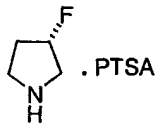


1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17 g, 0.88 mmol) was added to a stirred suspension of Intermediate 7 (0.20 g, 0.732 mmol) and 1-hydroxybenzotriazole (0.134 g, 0.878 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h to obtain a clear solution. Pyrrolidine (0.068 g, 0.951 mmol) was further added followed by addition of triethylamine (0.11 g, 1.098 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. It was then diluted with CH_2Cl_2 (25 ml) and washed successively with 10% HCl solution, water, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue obtained was purified by silica gel column chromatography using 1 % methanol in CH_2Cl_2 to afford the desired compound as a thick oil (0.25 g, 98 %); IR (KBr): 2975, 2877, 1729, 1710, 1643, 1438, 1170, 1051, 1020

cm^{-1}; ^{1}HNMR (300 MHz , $CDCl_3$) δ 0.96-1.03 (m, 1H), 1.15-1.24 (m, 1H), 1.43 (s, 9H), 1.69-1.81 (m, 2H), 1.82-2.02 (m, 4H), 3.38-3.64 (m, 4H), 3.66 (s, 3H), 4.44 (dd, *J* = 8.1, 6 .0 Hz, 1H), 5.44 (d, *J* = 8.1 Hz, 1H).

Intermediate 17

(3*S*)-3-Fluoropyrrolidine *p*-toluenesulfonate



Step 1: *tert*-Butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate: A solution of di-*tert*-butyldicarbonate (1.5 g, 6.81 mmol) in THF (5.0 ml) was added to a stirred solution of (*R*)-(+)-3-hydroxypyrrolidine (540 mg, 6.19 mmol) and triethylamine (940 mg, 9.29 mmol) in THF (10 ml) at 0 °C. The reaction mixture was further stirred for 4 h at the same temperature. THF was removed under reduced pressure and the residue was dissolved in dichloromethane (100 ml) and washed with 1*N* HCl solution (2 x 25 ml), saturated aqueous $NaHCO_3$ (25 ml), water (20 ml), brine (20 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using 4 % methanol in dichloromethane to afford 1.1 g (94 %) of the product as a colourless liquid; IR (neat) 3422, 2977, 1676, 1420, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.81 (br s, 1H), 1.90-1.99 (m, 2H), 3.33-3.99 (m, 4H), 4.44-4.79 (m, 1H).

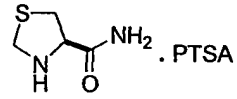
Step 2: *tert*-Butyl (3*S*)-3-fluoropyrrolidine-1-carboxylate: Diethylaminosulfur trifluoride (1.0 g, 6.49 mmol) was added to a stirred solution of Step 1 intermediate (800 mg, 4.27 mmol) in dichloroethane (15 ml) at - 40 °C. The reaction mixture was further stirred at the same temperature for 2 h and at RT for 15 h .The mixture was further diluted with chloroform (100 ml) and saturated $NaHCO_3$ solution (20 ml) and stirred for 10 min. The layers were separated and the aqueous layer was extracted with chloroform (2 x 50 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml) and dried ($NaSO_4$). The solvent was evaporated under reduced pressure and the residue obtained was purified by silica gel column chromatography using 8 % ethyl acetate in hexanes to afford 612 mg (75 %) of the product as a brown liquid; IR (neat) 3500, 2978, 1698, 1407 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s,

9H), 1.92-2.04 (m, 1H), 2.17-2.28 (m, 1H), 3.44-3.76 (m, 4H), 5.11, 5.28 (2t, J = 3.3, 3.3 Hz, 1H).

Step 3: *p*-Toluenesulfonic acid monohydrate (1.2 g, 6.34 mmol) was added to a stirred solution of Step 2 intermediate (800 mg, 4.22 mmol) in acetonitrile (10 ml) .The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue obtained was triturated with diethyl ether to give 1.01 g (91 %) of the product as a hygroscopic solid; IR (neat) 3443, 3019, 2783, 1626, 1434, 1215, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03-2.25 (m, 2H), 2.29 (s, 3H), 3.19-3.41 (m, 4H), 5.3, 5.51 (2t, J = 3.9, 3.3 Hz, 1H), 7.1 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 8.85 (br s, 1H), 9.1 (br s, 1H).

Intermediate 18

(4*S*)-1,3-thiazolane-4-carboxamide



Step 1: Preparation of (4*S*)-1,3-thiazolane-4-carboxylic acid: This intermediate was prepared from L-cysteine hydrochloride using a literature procedure (*J. Am. Chem. Soc*, **1937**, *59*, 200-206).

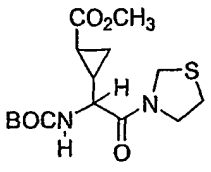
Step 2: Preparation of (4*S*)-*N*-(*tert*-Butoxycarbonyl)-1,3-thiazolane-4-carboxylic acid: A solution of di-*tert*-butyldicarbonate (21.3 g, 97.7 mol) in 50 ml was added to a stirred solution of step 1 Intermediate (10 g, 0.075 mol) and triethylamine (18.98 g, 0.188 mol) in 50 % aq. acetonitrile (100 ml) and the solution was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was acidified with 1*N* HCl to pH 3-4. The suspension was extracted with dichloromethane (2 x 100 ml) and the combined organic extracts were washed with water (2 x 100 ml), brine (100 ml) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was triturated with *n*-pentane to give 17.5 g (100 %) of the product as a white solid. IR (KBr) 3377-2704 (br), 1746, 1634, 1417, 1367, 1309, 1216, 1119, 1142, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 3.24-3.33 (m, 2H), 4.42-4.84 (m, 3H), 5.26 (brs, 1H).

Step 3: Preparation of (4*S*)-*N*-(*tert*-Butoxycarbonyl)-1,3-thiazolane-4-carboxamide: To a stirred and cooled (-15 °C) solution of step 2 intermediate (10 g, 64.37 mmol) and triethylamine (7.15 g, 70.79 mmol) in THF (100 ml) was added ethyl chloroformate (7.68 g, 70.79 mmol) to result a white precipitate. The mixture was stirred at the same temperature for 30 min and 30 % aqueous NH_4OH (100 ml) solution was added drop-wise over a period of 20 min. The temperature of reaction mixture was slowly raised to room temperature and further stirred for 18 h. The mixture was extracted with dichloromethane (2 x 100 ml) and the combined organic extracts were washed with brine (100 ml) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was triturated with *n*-pentane (50 ml) to give 7.1 g (71 %) of the product as a white solid. IR (KBr) 3406, 1666, 1405, 1365, 1163, 1109, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9H), 3.20-3.51 (br m, 2H), 4.51-4.54 (br m, 2H), 5.61 (br, m, 1H), 6.50 (br s, 2H).

Step 4: *p*-Toluenesulfonic acid monohydrate (1.31 g, 6.88 mmol) was added to a stirred solution of Step 3 intermediate (1.0 g, 4.30 mmol) in acetonitrile (20 ml) .The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure to give a viscous residue. The residue was triturated with diethyl ether (25 ml) to give 1.2 g (91 %) of the product as an off-white solid; ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.09 (dd, J = 11.7, 6.9 Hz, 1H), 3.41 (dd, J = 7.2, 11.7 Hz, 1H), 3.53 (br s, 1H), 4.26 (dd, J = 9.9, 15.3 Hz, 2H), 4.4 (t, J = 6.9 Hz, 1H), 7.1 (d, J = 7.5 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.81 (br s, 1H), 8.03 (br s, 1H), 9.70 (br s, 1H).

Intermediate 19

Methyl (1*RS*,2*RS*)-2-((1*RS*)-1-(*tert*-butoxycarbonyl)amino-2-oxo-2-(1,3thiazolan-yl) ethyl) cyclopropane-1-carboxylate

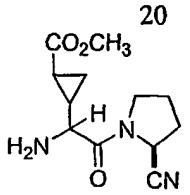


N-methylmorpholine (389 mg, 3.84 mmol) and pivaloyl chloride (243 mg, 2.01 mmoles) were added successively to a stirred and cooled (10 °C) solution of Intermediate 2 (500 mg, 1.83 mmol) in ethyl acetate(10 ml) to result a white precipitate. The mixture was further stirred at the same temperature for 30 min. Thiazolidine (180 mg, 2.01 mmol) was then added and the temperature was gradually allowed to come to room temperature and stirring was continued for another 1.5 h. The reaction mixture was diluted with ethyl acetate (200 ml), washed successively with 1*N* HCl solution, saturated $NaHCO_3$ solution, and brine and dried over anhy Na_2SO_4 .The solvent was evaporated under reduced pressure to afford a yellow residue. The residue was purified by silica gel column chromatography using 0.5 % methanol in dichloromethane to give 451 mg (71 %) the product as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96-1.03 (m, 1H), 1.19-1.26 (m, 1H), 1.43 (s, 9H), 1.72-1.80 (m, 2H), 3.03 (t, 1H) , 3.12 (t, 1H), 3.67 (s, 3H) 3.76-3.94 (m, 2H), 4.44-4.54 (m, 2H), 4.64-4.67 (m, 1H), 5.37-5.40 (d, J = 9 Hz, 1H).

Examples

Example 1

Methyl (1*SR*,2*SR*)-2-{(1*SR*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} cyclopropane-1-carboxylate



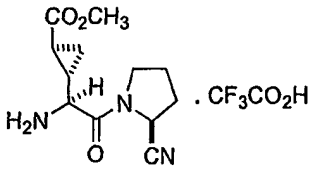
Step 1: Methyl (1*SR*,2*SR*)-2-{(1*SR*)-1-(*tert*-butoxycarbonyl)amino-2-(2*S*)-2-carbamoyl pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate: This intermediate was prepared by the coupling reaction of Intermediate 2 (2.0 g, 7.31 mmol) with L-prolinamide (1.0 g, 8.78 mmol) using EDCI (1.68 g, 8.78 mmol) and as described in Intermediate 9 to give 2.4 g (88 %) of the product as white solid; IR (KBr) 3340, 2979, 1694, 1645, 1439, 1172, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.04 (m, 1H), 1.19-1.26 (m, 1H), 1.41, 1.43(s, 9H), 1.66-1.78 (m, 2H), 1.91-2.05 (m, 3H), 2.14-2.36 (m, 1H), 3.66, 3.68 (s, 3H), 3.49-3.88 (m, 2H), 4.12, 4.48 (t, J = 8.1 Hz, 1H), 4.57-4.62 (m, 1H), 5.33 (br s, 2H), 6.62, 6.84 (br s, 1H).

Step 2: Methyl (1*RS*,2*RS*)-2-{(1*RS*)-1-(*tert*-Butoxycarbonyl)amino-(2*S*)-2-cyano pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate: To a stirred and cooled (0 °C) solution of Step 1 intermediate (0.45 g, 1.21 mmol) in pyridine (5 ml) was added $POCl_3$ (0.453 ml, 4.87 mmol)) and the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was poured onto ice-cold water (100 ml) and the resulting solution was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with 1*N* HCl solution, saturated $NaHCO_3$ solution, water, and dried Na_2SO_4). The solvent was evaporated under reduced pressure to give to 390 mg (90 %) of the product as a viscous liquid; IR (neat) 3331, 2978, 2242, 1725, 1657, 1427, 1127, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.04 (m, 1H), 1.22-1.28 (m, 1H), 1.42, 1.44(s, 9H), 1.66-1.78 (m, 2H), 2.18-2.32 (m, 4H), 3.52-3.57 (m, 1H), 3.66, 3.67 (s, 3H), 3.84-3.87 (m, 1H), 4.35-4.43 (m, 1H), 4.68, 4.76 (m, 1H), 5.33, 5.38 (m, 1H).

Step 3: To a solution of Step 2 intermediate (390 mg, 1.10 mmol) in dry dichloromethane (2 ml) was added trifluoroacetic acid (2.5 ml) at 0 °C and the solution was stirred for 1 h at the same temperature. Diethyl ether was added to the reaction mixture to precipitate the product. The product was dissolved in 10 ml saturated $NaHCO_3$ solution, extracted with dichloromethane and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 110 mg (39 %) of the product as a white hygroscopic solid; IR (neat) 3368, 2927, 2224, 1724, 1650, 1434, 1176, 926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03-1.08 (m, 1H), 1.16-1.26 (m, 1H), 1.60 (br s, 2H), 1.64-1.78 (m, 1H), 2.16-2.32 (m, 5H), 3.43 (dd, J = 6.34, 3.3 Hz, 1H), 3.51-3.69 (m, 1H), 3.67, 3.68 (s, 3H), 3.72-3.75 (m, 1H), 4.72-4.79 (m, 1H).

Example 2

Methyl (1*S*, 2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} cyclopropane-1-carboxylate trifluoroacetate

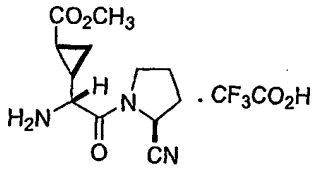


Step 1: Methyl (1*S*,2*S*)-2-{(1*S*)-1-(*tert*-Butoxycarbonyl)amino-2-(2*S*)-2-carbamoyl pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate: To a stirred and cooled (0 °C) solution of Intermediate 9 (0.3 g, 0.8 mmol) in pyridine (4.5 ml) was added $POCl_3$ (302 µl, 3.24 mmol)) and the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was poured onto ice-cold water (100 ml) and the resulting solution was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with 1*N* HCl, saturated $NaHCO_3$ solution, water, brine, and dried over anhy Na_2SO_4. The residue obtained after evaporation of the solvent was used as such for the next step; IR (neat) 3339, 2979, 2242, 1718, 1655, 1509, 1425, 1367, 1249, 1173, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.06 (m, 1H), 1.24-1.42 (m, 1H), 1.43,1.47(s, 9H), 1.68-1.76 (m, 1H), 1.77-1.82 (m, 1H), 2.15-2.32 (m, 4H), 3.68 (s, 3H), 3.69-3.71 (m, 2H), 4.38 (dd, *J* = 6.3, 1.8 Hz, 1H), 4.76-4.78 (m, 1H) 5.31, 5.33 (s, 1H).

Step 2: To a solution of step 1 intermediate (290 mg, 0.82 mmol) in dry dichloromethane (2 ml)was added trifluoroacetic acid (2.5 ml) at 0°C and the solution was stirred for 1 h at the same temperature. Diethyl ether was added to the reaction mixture to precipitate the product. The product was collected by filtration to give 120 mg (39 %) of the product as a white hygroscopic solid; IR (neat) 3401, 1728, 1668, 1511, 1439, 1409, 1347, 1202, 1180, 1136, 760 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23-1.43 (m, 2H), 1.85 (m, 2H), 2.07 (m, 2H), 2.27 (m, 2H), 3.63 (m, 2H), 3.65 (s, 3H), 4.16 (d, *J* = 9 Hz, 1H), 4.78 (m, 1H).

Example 3

Methyl (1*R*, 2*R*)-2-{(1*R*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} cyclopropane-1-carboxylate trifluoroacetate



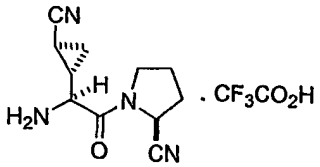
Step 1: Methyl(1*R*,2*R*)-2-{(1*R*)-1-(*tert*-butoxycarbonyl)amino-2-[(2*S*)-2-carbamoyl pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate: This intermediate was prepared from Intermediate 10 (320 mg, 0.86 mmol) using $POCl_3$ (0.32 ml, 3.46

mmol) in pyridine (4 ml) as described in Example 1, Step 1 to give 275 mg (90 %) of the product as a crystalline solid; IR (KBr) 3325, 2978, 2243, 1732, 1709, 1643, 1518, 1437, 1366, 1255, 1173, 1090, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-1.01 (m, 1H), 1.17-1.28 (m, 1H), 1.42, 1.44 (s, 9H), 1.63-1.76 (m, 2H), 2.17-2.34 (m, 4H), 3.52-3.57 (m, 1H), 3.66 (s, 3H), 3.81-3.87 (m, 1H), 4.40 (dd, J = 7.8, 5.4 Hz, 1H), 4.67-4.69 (m, 1H), 5.35, 5.38 (s, 1H).

Step 2: Reaction of step 1 intermediate with TFA (1.5 ml) as described in Example 1, Step 2 gave 120 mg (42 %) of the product as a crystalline hygroscopic solid; IR (neat) 3020, 1728, 1674, 1521, 1439, 1215, 1139, 757 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.24-1.39 (m, 2H), 1.83 (m, 2H), 2.11 (m, 2H), 2.27 (m, 2H), 3.52 (m, 1H), 3.63 (s, 3H), 3.71 (m, 1H), 4.07 (d, J = 9.3 Hz, 1H), 5.75 (m, 1H).

Example 4

1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-cyanocyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate



Step 1: 1-{(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-carbamoylcyclopropyl]-ethanoyl}pyrrolidine-2-(2*S*)-carboxamide: To a stirred solution of Intermediate 9 (200 mg, 0.54 mmol) in THF (5.0 ml) was added aqueous ammonia (5.0 ml) and the solution was stirred at room temperature for 144 h. The solvent was evaporated under reduced pressure and the residue obtained was diluted with water (25 ml). The solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product obtained was purified by silica gel column chromatography using 8 % methanol in dichloromethane to give 130 mg (67 %) of the product as an off-white solid; IR (KBr) 3402, 2978, 1668, 1645, 1517, 1447, 1428, 1367, 1274, 1166, 1016, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.94 (m, 1H), 1.18-1.25 (m, 1H), 1.43 (s, 9H), 1.66-1.85 (m, 3H), 1.99-2.21 (m, 3H), 3.60-3.80 (m, 2H), 4.42-4.52 (m, 1H),

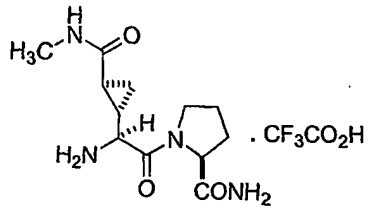
4.70 (br t, J = 6.9Hz, 1H), 5.50 (br d, J = 7.8 Hz, 1H), 5.72 (br s, 1H), 6.04 (br s, 1H), 6.38 (br s, 1H), 6.62 (br s, 1H).

Step2:1-{(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-cyanocyclopropyl]ethanoyl} pyrrolidine-2-(2*S*)-carbonitrile: Reaction of intermediate step 1 (120 mg, 0.338 mmol) with $POCl_3$ (0.251 ml, 2.708 mmol)) in pyridine (4 ml) as described in Example 1, Step 1 gave 100 mg (92 %) of the product as a semi-solid; IR (neat) 3337, 2979, 2931, 2241, 1708, 1654, 1513, 1427, 1367, 1250, 1163, 1024, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.20 (m, 1H), 1.33-136 (m, 1H), 1.43, 1.47 (s, 9H), 1.48-1.55 (m, 1H), 1.88-1.96 (m, 1H), 2.14-2.38 (m, 4H), 3.65-3.69 (m, 2H), 4.31 (dd, J = 8.1, 7.5 Hz, 1H), 4.74-4.78 (m, 1H), 5.35 (br d, J = 7.2 Hz, 1H).

Step 3: Reaction of Step 2 intermediate (90 mg, 0.28 mmol) with TFA (0.350 ml) as described in Example 1, Step 2 gave 70 mg (74 %) of the product as a crystalline hygroscopic solid; IR (neat) 3444, 2978, 2245, 1666, 1595, 1516, 1442, 1180, 1208, 1140, 836, 799, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.42-1.50 (m, 1H), 1.54-1.61 (m, 1H), 1.78-1.85 (m, 1H), 1.98-2.19 (m, 3H), 2.25-2.38 (m, 2H), 3.55-3.70 (m, 2H), 4.06 (d, J = 9.3 Hz, 1H), 4.78 (m, merged with HOD peak, 1H).

Example 5

1-{(2*S*)-amino-2-[(1*S*, 2*S*)-2-methylcarbamoylcyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide trifluoroacetate



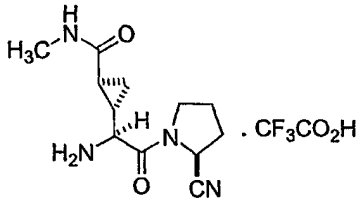
Step 1: 1-{(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclopropyl]acetyl}pyrrolidine-2-(2*S*)-carboxamide: To a stirred solution of Intermediate 9 (500 mg, 1.35 mmol) in THF (4.0 ml) was added 40 % aqueous methylamine (4.0 ml) and the solution was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure and the residue obtained was diluted with water (20 ml). The solution was extracted with dichloromethane (3 x 50 ml) and the combined organic

extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography using 5 % methanol in dichloromethane to give 400 mg (80 %) of the product as an off-white solid; IR (KBr) 3406, 2978, 1688, 1645, 1441, 1367, 1250, 1166, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76-0.82 (m, 2H), 1.38 (s, 9H), 1.49-1.51 (m, 1H), 1.58-1.62 (m, 1H), 1.77-2.01 (m, 4H), 2.56 (d, J = 4.8 Hz, 3H), 3.50-3.58 (m, 2H), 3.97-4.02 (m, 1H), 4.19-4.23 (m, 1H), 6.95 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 7.84 (d, J = 4.2 Hz, 1H).

Step 2: Reaction of Step 1 intermediate (125 mg, 0.33 mmol) with TFA (0.350 ml, 4.54) as described in Example 1, Step 2 gave 68 mg (52 %) of the product as a crystalline hygroscopic solid; IR (KBr) 3408, 1678, 1658, 1203, 1135 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6) δ 0.94-0.99(m, 2H), 1.52-1.55 (m, 1H), 1.78-1.86 (m, 2H), 1.92-1.98 (m, 2H), 2.09-2.13 (m, 1H), 2.6 (d, J = 4.8Hz, 3H), 3.44-3.46 (m, 1H), 3.63-3.68 (m, 1H), 4.26-4.37 (m, 2H), 7.07 (s, 1H), 7.52 (s, 1H), 7.84 (d, J = 4.2Hz, 1H), 8.17 (br s, 3H).

Example 6

1-{2(*S*)-2-Amino-2-[(1S,2S)-2-methylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate



Step 1: (2*S*)-1-{(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclo-propyl]ethanoyl}pyrrolidine-2-carboxamide: To a stirred solution of Intermediate 9 (500 mg, 1.35 mmol) in THF (4.0 ml) was added 40 % aqueous methylamine (4.0 ml) and the solution was stirred at room temperature for 15 h. The mixture was evaporated under reduced pressure and the residue obtained was diluted with water (20 ml). The solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product obtained was purified by silica gel column

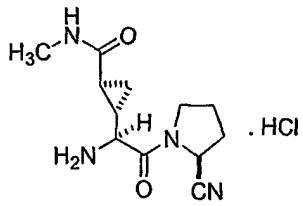
chromatography using 5 % methanol in dichloromethane gave 420 mg (84 %) of the product as an off-white solid; IR (KBr) 3406, 2978, 1688, 1645, 1441, 1367, 1250, 1166, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76-0.82 (m, 2H), 1.38 (s, 9H), 1.49-1.51 (m, 1H), 1.58-1.62 (m, 1H), 1.77-2.01 (m, 4H), 2.56 (d, J = 4.8 Hz, 3H), 3.50-3.58 (m, 2H), 3.97-4.02 (m, 1H), 4.19-4.23 (m, 1H), 6.95 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 7.84 (d, J = 4.2 Hz, 1H).

Step 2: (2*S*)-1-{(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclo-propyl]ethanoyl}pyrrolidine-2-carbonitrile: Reaction of Step 1 intermediate (160 mg, 0.434 mmol) with $POCl_3$ (0.161 ml, 1.73 mmol)) in pyridine (3 ml) as described in Example 1, Step 2 gave 95 mg (62 %) of the product as a semisolid; IR (neat) 3430, 3020, 1709, 1662, 1422,1216,758,669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88-0.95 (m, 2H), 1.23-1.32 (m, 1H), 1.43 (s, 9H), 1.64-1.78 (m, 1H), 2.04-2.31 (m, 4H), 2.79 (d, J = 4.8 Hz, 3H), 3.68-3.78 (m, 2H), 4.58 (t, J = 7.8 Hz, 1H), 4.73-4.76 (m, 1H), 5.30 (d, J = 7.2 Hz, 1H), 5.72-5.78 (m, 1H).

Step 3: Reaction of Example 5 step 2 intermediate (90 mg, 0.25 mmol) with TFA (0.350 ml, 4.54 mmol) as described in Example 1, Step 3 to give 87 mg (93 %) of the product as a crystalline hygroscopic solid; IR (neat) 3375, 2956, 2926, 1668, 1661, 1452, 1347, 1203, 1136, 837, 759, 723 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.82 (t, J = 7.5 Hz, 3H), 1.16-1.29 (m, 2H), 1.70-1.80 (m, 2H), 2.00-2.32 (m, 2H), 2.68 (s, 3H), 3.13 (t, J = 7.9 Hz, 2H), 3.58-3.67 (m, 2H), 4.17 (d, J = 8.7 Hz, 1H), 4.78-4.80 (m, 1H).

Example 7

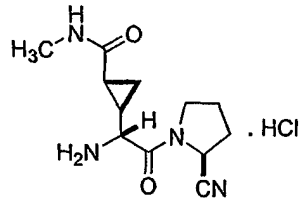
1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-methylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile hydrochloride



To a solution of intermediate from Example 5, Step 2 (150 mg, 0.428 mmol) in ethyl acetate (10 ml) was added a saturated solution of HCl in ethyl acetate (1.0 ml). The solution was stirred for 2 h at 0 °C. The precipitated solid was filtered and washed with ethyl acetate to give 80 mg (66 %) of the product as a white hygroscopic solid; IR (KBr) 3424, 2982, 1651, 1556, 1501, 1440, 1349, 1238, 1027 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.15-1.28 (m, 2H), 1.70-1.82 (m, 2H), 2.00-2.19 (m, 2H), 2.25-2.35 (m, 2H), 2.68 (s, 3H), 3.57-3.70 (m, 2H), 4.17 (d, J = 8.7 Hz, 1H)

Example 8

1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-methylcarbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile hydrochloride



Step 1: (2*S*)-1-{(2*R*)-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2R)-2-methylcarbamoylcyclo-propyl]ethanoyl}pyrrolidine-2-carboxamide: To a stirred solution of Intermediate 10 (500 mg, 1.35 mmol) in THF (4.0 ml) was added 40 % aqueous methylamine (4.0 ml) and the solution was stirred at room temperature for 15 h. The mixture was evaporated under reduced pressure and the residue obtained was diluted with water (20 ml). The solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product obtained was purified by silica gel column chromatography using 5 % methanol in dichloromethane gave 420 mg (84 %) of the product as an off-white solid; IR (KBr) 3406, 2978, 1688, 1645, 1441, 1367, 1250, 1166, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.88 (m, 2H), 1.17-1.25 (m, 2H), 1.41, 1.43 (s, 9H), 1.57-2.20 (m, 6H), 2.80 (d, J = 4.8 Hz, 3H), 3.65-3.68 (m, 2H), 4.46-4.50 (m, 1H), 4.61 (t, J = 7.8 Hz, 1H), 5.52 (s, 1H), 6.33 (s, 1H), 6.50 (s, 1H).

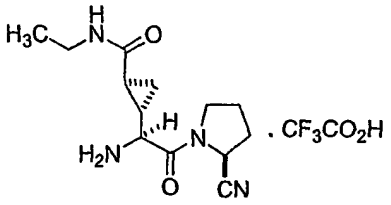
Step 2: (2*S*)-1-{(2*R*)-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2-methylcarbamoylcyclo-propyl]ethanoyl}pyrrolidine-2-carbonitrile: Reaction of Step 1

intermediate (160 mg, 0.434 mmol) with $POCl_3$ (0.161 ml, 1.73 mmol)) in pyridine (3 ml) as described in Example 1, Step 2 gave 95 mg (62 %) of the product as a semisolid; IR (neat) 3430, 3020, 1709, 1662, 1422,1216, 758, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88-0.95 (m, 2H), 1.23-1.32 (m, 1H), 1.43 (s, 9H), 1.64-1.78 (m, 1H), 2.04-2.31 (m, 4H), 2.79 (d, J = 4.8 Hz, 3H), 3.68-3.78 (m, 2H), 4.58 (t, J = 7.8 Hz, 1H), 4.73-4.76 (m, 1H), 5.30 (d, J = 7.2 Hz, 1H), 5.72-5.78 (m, 1H).

Step 3: To a solution of Step 2 intermediate (150 mg, 0.428 mmol) in ethyl acetate (10 ml) was added a saturated solution of HCl in ethyl acetate (1 ml). The solution was stirred at 0 °C for 2 h. The precipitated solid was filtered and washed with ethyl acetate to give 80 mg (65.5 %) of the product as a white hygroscopic solid; IR (KBr) 3399, 2926, 2246, 1658, 1568, 1448, 1349, 1248, 1191, 1160, 1063 cm^{-1}; 1H NMR (300 MHz, D_2O) 1.13-1.26 (m, 2H), 1.65-1.79 (m, 2H), 2.08-2.18 (m, 2H), 2.24-2.32 (m, 2H), 2.67 (s 3H), 3.45-3.57 (m, 1H), 3.71-3.78 (m, 1H), 4.07 (d, J = 9.0 Hz, 1H), 4.72-4.80 (m, 1H).

Example 9

1-{(2S)-2-Amino-2-[(1S,2S)-2-ethylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2S)-carbonitrile trifluoroacetate



Step 1: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-ethylcarbamoylcyclopropyl] ethanoyl}-pyrrolidine-2-(2*S*)-carboxamide: To a solution of Intermediate 11 (500 mg, 1.406 mmol) in dichloromethane (50 ml) was added 1-hydroxy benzotriazole (228 mg, 1.687 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg, 1.687 mmol), ethylamine (127 mg, 2.813 mmol) and finally triethylamine (285 mg, 2.813 mmol). The reaction mixture was stirred for 50 h at room temperature. The mixture was diluted with dichloromethane (300 ml) and washed with 1*N* HCl, saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue obtained was

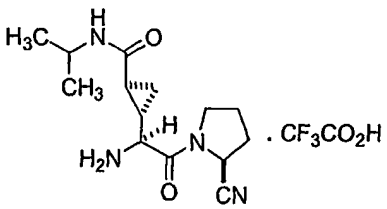
purified by silica gel column chromatography using 4 % methanol in dichloromethane to give 153 mg (28 %) of the product as a white solid; IR (neat) 3320, 2977, 2932, 1686, 1645, 1548, 1440, 1248, 1167, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-0.88 (m, 2H), 1.12 (t, J = 6.9 Hz, 3H), 1.42,1.43 (s, 9H), 1.54-1.60 (m, 1H), 1.76-1.86 (m, 1H), 2.00-2.40 (m, 4H), 3.27 (q, J = 5.4 Hz, 2H), 3.65-3.70 (m, 2H), 4.45-4.52 (m, 1H), 4.63 (t, J = 7.2 Hz, 1H), 5.30-5.40 (m, 1H), 5.44 (br s, 1H), 6.32 (br s, 1H), 6.46 (br s, 1H).

Step 2: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-ethylcarbamoylcyclopropyl] ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 Intermediate (145 mg, 0.379 mmol) with $POCl_3$ (232 mg, 1.516 mmol)) in pyridine (3 ml) as described in Example 1 ,step 1 gave 87 mg (63%) of the product as a white solid; IR (neat) 3324, 2975, 2926, 1695, 1548, 1428, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.96 (m, 2H), 1.14 (t, J = 7.2 Hz, 2H), 1.23-1.38 (m, 1H), 1.431.45 (s, 9H), 1.72-1.82 (m, 1H), 2.14-2.32 (m, 4H), 3.22-3.32 (m, 2H), 3.64-3.76 (m, 2H), 4.57 (t, J = 7.5 Hz, 1H), 4.72-4.78 (m, 1H), 5.26-5.32 (m, 1H), 5.72-5.78 (m, 1H).

Step 3: Reaction of Step 2 intermediate (80 mg, 0.219 mmol) with TFA (0.700ml, 9.08 mmol) as described in Example 1, Step 2 gave 23 mg (28 %) of the product as a crystalline hygroscopic solid; IR (neat) 3368, 2955, 2919, 1667, 1556, 1452, 1203, 1186, 1136, 836 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.03 (t, J = 7.2 Hz, 3H), 1.16-1.28 (m, 2H), 1.69-1.84 (m, 2H), 2.00-2.40 (m, 2H), 2.24-2.36 (m, 2H), 3.14 (q, J = 7.5 Hz, 2H), 3.63 (q, J = 7.5 Hz, 2H), 4.19 (d, J = 8.7 Hz, 1H), 4.72-4.80 (m, 1H).

Example 10

1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-isopropylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate



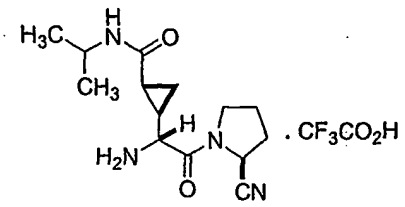
Step 1: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-isopropylcarbamoylcyclo- propyl]ethanoyl}-pyrrolidine-2-(2S)-carboxamide: Reaction of Intermediate 11 (200 mg, 0.562 mmol) with isopropylamine (66 mg, 1.124 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (129 mg, 0.675 mmol), 1-hydroxybenzotriazole (91 mg ,0.675 mmol), and triethylamine (114 mg,1.124 mmol) in dichloromethane (30 ml) gave 55 mg (25 %) of the product as a white hygroscopic solid; IR (KBr) 3323, 2974, 1689, 1643, 1544, 1420, 1248, 1168 cm^{-1}; ^1H NMR (300 MHz ,$CDCl_3$) δ 0.80-0.87 (m, 1H), 1.13 (d, J= 5.1 Hz, 3H), 1.15 (d, J = 5.4 Hz, 3H), 1.15-1.26 (m, 2H), 1.43 (s, 9H), 1.76-1.85 (m, 1H), 2.00-2.19 (m, 4H), 3.65-3.69 (m, 2H), 3.99-4.11 (m, 1H), 4.46-4.54 (m, 1H), 4.62 (t, J = 7.8 Hz, 1H), 5.31-5.34 (m, 2H), 6.26-6.33 (m, 2H).

Step 2: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-isopropylcarbamoylcyclo- propyl]ethanoyl}-pyrrolidine-2-(2S)-carbonitrile: Reaction of Step 1 intermediate (110 mg, 0.277 mmol) with $POCl_3$ (0.103 ml, 1.109 mmol)) in pyridine (3 ml) as described in Example 1, Step 1 gave 85 mg (81%) of the product as a semisolid; IR (neat) 3312, 2975, 2930, 1691, 1647, 1544, 1427, 1367, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-0.92 (m, 1H), 1.12 (d, J =4.5 Hz, 3H), 1.14 (d, J = 4.5 Hz, 3H), 1.20-1.40 (m, 2H), 1.43 (s, 9H), 1.72-1.84 (m, 1H), 2.10-2.34 (m, 4H), 3.62-3.78 (m, 2H), 4.00-4.18 (m, 1H), 4.56 (t, J = 6.9 Hz, 1H), 4.72-4.78 (m, 1H), 5.32 (d, J = 7.5 Hz, 1H), 5.63 (d, J = 7.2 Hz, 1H).

Step 3: Reaction of Step 2 intermediate (80 mg, 0.211 mmol) with TFA (0.350 ml, 4.54 mmol) as described in Example 1, Step 2 gave 38 mg (35 %) of the product as a crystalline hygroscopic solid; IR (KBr) 3572, 3437, 2975, 2930, 1651, 1204 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.07 (q, J = 1.8 Hz, 6H), 1.15-1.28 (m, 2H), 1.68-1.81 (m, 2H), 2.02-2.34 (m, 4H), 3.61-3.67 (m, 2H), 3.82-3.91 (m, 1H), 4.19 (d, J = 9.3 Hz, 1H), 4.72-4.80 (m, 1H).

Example 11

1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-isopropylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate



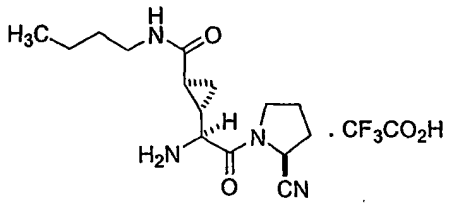
Step 1: 1-{2-(2*R*)-2-(*tert*-Butoxycarbonyl) amino-2-[(1*R*,2*R*)-2-isopropylcarbamoylcyclo propyl]acetyl}-pyrrolidine-2-(2*S*)-carboxamide: Reaction of Intermediate 12 (375 mg, 1.055 mmol) with isopropylamine (125 mg, 2.110 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (243 mg, 1.266 mmol), 1-hydroxybenzotriazole (171 mg ,1.266 mmol), and triethylamine (213 mg, 2.110 mmol) in dichloromethane (50 ml) gave 157 mg (37 %) of the product as a white hygroscopic solid; IR (KBr) 3323, 2974, 1689, 1643, 1544, 1420, 1248, 1168 cm^{-1}; ^1H NMR (300 MHz ,$CDCl_3$) δ 0.83-0.91 (m, 1H), 1.14 (d, J = 6.6 Hz, 6H), 1.12-1.35 (m, 2H), 1.42,1.44 (s, 9H), 1.65-1.75 (m, 1H), 1.98-2.10 (m, 3H), 2.30-2.40 (m, 1H), 3.50-3.60 (m, 1H), 3.82-3.90 (m, 1H), 4.00-4.20 (m, 2H), 4.50-4.60 (m, 1H), 5.48-5.56 (m, 1H), 6.66-6.84 (m, 1H).

Step 2: 1-{2-(2*R*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2-isopropylcarbamoylcyclo propyl]acetyl}-pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (150 mg, 0.378 mmol) with $POCl_3$ (0.140 ml, 1.513 mmol)) in pyridine (3 ml) as described in Example 1, Step1 gave 115 mg (80 %) of the product as a white solid; IR (neat) 3306, 2928, 2443, 1693, 1645, 1430, 1368, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.90 (m, 2H), 1.13 (d, J = 6.0 Hz, 6H), 1.10-1.70 (m, 2H), 1.42,1.44 (s, 9H), 2.10-2.40 (m, 2H), 3.52-3.62 (m, 1H), 3.80-3.88 (m, 1H), 3.98-4.18 (m, 1H), 4.37-4.42 (m, 1H), 4.66 (d, J = 5.4 Hz, 1H), 5.38 (d, J = 7.8 Hz, 1H), 5.49 (d, J = 8.1 Hz, 1H).

Step 3: Reaction of Step 2 intermediate (110 mg, 0.291 mmol) with TFA (0.700 ml, 9.08 mmol) as described in Example 1, Step 2 gave 0.043 g (38 %) of the product as a crystalline hygroscopic solid. IR (KBr) 3400, 2922, 2848, 1667, 1402, 1203, 1133 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.06 (q, J = 3.3 Hz, 6H), 1.10-1.28 (m, 2H), 1.60-1.72 (m, 2H), 2.09-2.15 (m, 2H), 2.20-2.30 (m, 2H), 3.46-3.90 (m, 3H), 4.10 (d, J = 8.4 Hz, 1H), 4.72-4.86 (m, 1H).

Example 12

1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-butylcarbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile trifluoroacetate



Step 1: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-butylcarbamoylcyclopropyl]ethanoyl}-pyrrolidine-2-(2S)-carboxamide: Reaction of Intermediate 11 (500 mg, 1.406 mmol) with n-butylamine (206 mg, 2.813 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg, 1.687 mmol), 1-hydroxybenzotriazole (228 mg, 1.687 mmol), and triethylamine (285 mg, 2.813 mmol) in dichloromethane (50 ml) gave 0.197 g (34 %) of the product as a white hygroscopic solid IR (KBr) 3229, 3208, 2959, 2930, 1665, 1688, 1643, 1544, 1367, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.95 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H), 1.19-1.63 (m ,6H), 1.42,1.44 (s, 9H), 1.77-1.86 (m, 1H), 2.00-2.24 (m, 4H), 3.23 (q, J = 6.0 Hz, 2H), 3.65-3.69 (m, 2H), 4.46-4.56 (m, 1H), 4.63 (t, J = 7.5 Hz, 1H), 5.31-5.36 (m, 2H), 6.24-6.30 (m, 1H), 6.40-6.46 (m, 1H).

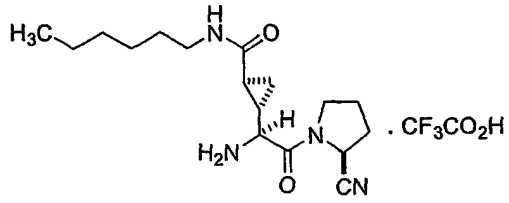
Step 2: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-butylcarbamoylcyclopropyl]ethanoyl}-pyrrolidine-2-(2S)-carbonitrile: Reaction of Step 1 intermediate (190 mg, 0.462 mmol) with $POCl_3$ (0.172 ml, 1.85 mmol)) in pyridine (3 ml) as described in Example 1, Step 1 gave 123 mg (68 %)of the product as a white solid; IR (neat) 3321, 2960, 2931, 1693, 1651, 1520, 1428, 1284, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.96 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H), 1.22-1.52 (m ,6H), 1.43,1.45 (s, 9H), 1.72-1.82 (m, 1H), 2.14-2.32 (m, 4H), 3.12-3.33 (m, 2H), 3.60-3.76 (m, 2H), 4.56 (t, J = 6.6 Hz, 1H), 4.73-4.78 (m, 1H), 5.26-5.34 (m, 1H), 5.72-5.80 (m, 1H).

Step 3: Reaction of Step 2 intermediate (120 mg, 0.305 mmol) with TFA (0.700 ml, 9.08 mmol) as described in Example 1, Step 2 gave 0.061 g (49 %) of the product as

a crystalline hygroscopic solid; IR (neat) 3320, 2960, 2930, 1667, 1449, 1202, 1136 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.82 (t, J = 7.5 Hz, 3H), 1.17-1.28 (m, 4H), 1.36-1.48 (m, 2H), 1.70-1.84 (m, 2H), 2.04-2.31 (m, 4H), 3.13 (t, J = 7.9 Hz, 2H), 3.60-3.66 (m, 2H), 4.22 (d, J = 8.7 Hz, 1H), 4.72-4.80 (m, 1H).

Example 13

1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-hexylcarbamoylcyclopropyl]acetyl}-pyrrolidine-2(*S*)-carbonitrile trifluoroacetate



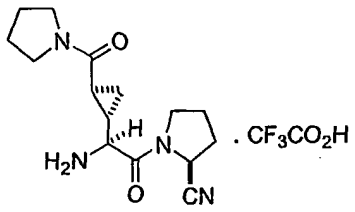
Step 1: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-hexylcarbamoylcyclopropyl]ethanoyl}-pyrrolidine-2-(2S)-carboxamide: Reaction of Intermediate 11 (500 mg, 1.406 mmol) with n-hexylamine (171 mg, 1.687 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg, 1.687 mmol), 1-hydroxybenzotriazole (228 mg, 1.687 mmol), and triethylamine (285 mg, 2.813 mmol) in dichloromethane (50ml) gave 141 mg (23 %) of the product as a white hygroscopic solid IR (neat) 3329, 3207, 2957, 2930, 1689, 1642, 1546, 1437, 1305, 1171, 1920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-0.90 (m, 5H), 1.17-1.52 (m, 8H), 1.42,1.43 (s, 9H), 1.55-1.62 (m, 1H), 1.77-1.86 (m, 1H), 2.00-2.24 (m, 4H), 3.22 (qn, J = 5.7 Hz, 2H), 3.65-3.69 (m, 2H), 4.48 (brs, 1H), 4.63 (t, J = 7.5 Hz, 1H), 5.30-5.40 (m, 2H), 6.26 (brs, 1H), 6.41 (brs, 1H).

Step 2: 1-{2-(2S)-2-(*tert*-Butoxycarbonyl)amino-2-[(1S,2S)-2-hexylcarbamoylcyclopropyl]ethanoyl}-pyrrolidine-2-(2S)-carbonitrile: Reaction of Step 1 intermediate (135 mg, 0.307 mmol) with $POCl_3$ (0.114 ml, 1.23 mmol)) in pyridine (3 ml) as described in Example 1, Step 1 gave 103 mg (80 %) of the product as a semi-solid; IR (neat) 3310, 2957, 2929, 1689, 1651, 1550, 1430, 1248, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-0.93 (m, 5H), 1.20-1.47 (m, 8H), 1.43, 1.45 (s, 9H), 1.70-1.90 (m, 2H), 2.10-2.36 (m, 4H), 3.10-3.30 (m, 2H), 3.60-3.80 (t, J = 5.1 Hz, 1H), 4.72-4.80 (m, 1H), 5.28-5.32 (m, 1H), 5.72-5.80 (m, 1H).

Step 3: Reaction of Step 2 intermediate (95 mg, 0.226 mmol) with TFA (0.700 ml, 9.08 mmol) as described in Example 1, Step 2 to give 61 mg (62 %) of the product as a crystalline hygroscopic solid; IR (neat) 3313, 3098, 2957, 2930, 2859, 1666, 1555, 1451, 1203, 1184, 1136, 722 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.79 (t, J = 6.3 Hz, 3H), 1.14-1.28 (m, 8H), 1.40-1.48 (m, 2H), 1.68-1.85 (m, 2H), 2.00-2.20 (m, 2H), 2.24-2.36 (m, 2H), 3.12 (t, J = 6.6 Hz, 2H), 3.60-3.68 (m, 2H), 4.21 (d, J = 8.4 Hz, 1H), 4.72-4.80 (m, 1H).

Example 14

1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-azolanylcarbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile trifluoroacetate



Step 1: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(1-pyrrolidinylcarbonyl) cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide: Reaction of Intermediate 11 (1.0 g, 2.813 mmol) with pyrrolidine (240 mg, 3.376 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (647 mg, 3.376 mmol), 1-hydroxybenzotriazole (456 mg, 3.376 mmol), and triethylamine (569 mg, 5.626 mmol) in dichloromethane (100 ml) gave 500 mg (43 %) of the product as a white hygroscopic solid IR (neat) 3410, 3019, 2928, 1699, 1639, 1431, 1215, 1048, 757, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92-0.98 (m, 2H), 1.17-1.29 (m, 1H), 1.41, 1.43 (s, 9H), 1.78-2.09 (m, 8H), 2.32-2.37 (m, 1H), 3.42 (t, J = 5.8 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 3.68 (t, J = 7.5 Hz, 2H), 4.47 (t, J = 7.2 Hz, 1H), 4.59-4.62 (m, 1H), 5.25 (brs, 1H), 5.42 (d, J = 7.5 Hz, 1H), 6.57 (brs, 1H).

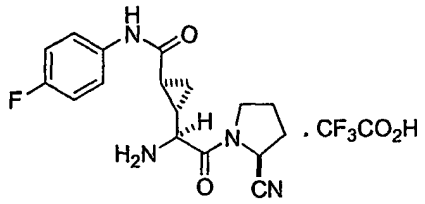
Step 2: (2*S*)-1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(1-pyrrolidinylcarbonyl) cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (125 mg, 0.3059 mmol) with $POCl_3$ (0.113 ml, 1.22 mmol)) in pyridine (3 ml) as described in Example 1, Step 1 gave 71 mg (60 %) of the

product as a semi-solid; IR (neat) 3328, 2981, 2884, 1779, 1705, 1652, 1575, 1453, 1260, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88-1.40 (m, 3H), 1.42, 1.43 (s, 9H), 1.70-2.30 (m, 9H), 3.20-3.34 (m, 2H), 3.39 (t, J = 6.6 Hz, 2H), 3.54-3.62 (m, 2H), 4.55-4.58 (m, 1H), 4.72-4.78 (m, 1H), 5.36 (d, J = 7.8 Hz, 1H).

Step 3: Reaction of Step 2 intermediate (150 mg, 0.384 mmol) with TFA (0.700 ml, 9.08 mmol) as described in Example 1, Step 2 gave 75 mg (48 %) of the product as a crystalline hygroscopic solid; IR (neat) 3400, 3172, 2921, 1656, 1625, 1445, 1202, 1176, 1143, 1021 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.20-1.24 (m, 2H),1.78-1.96 (m, 8H), 2.10 (q, J = 6.6 Hz, 2H), 2.27 (t, J = 6.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H), 3.46-3.72 (m, 4H), 4.32 (q, J = 7.5 Hz, 1H), 4.72-4.80 (m, 1H).

Example 15

1-{2-(2*S*)-Amino-2-[(1*S*,2*S*)-2-(4-fluorophenylcarbamoyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate



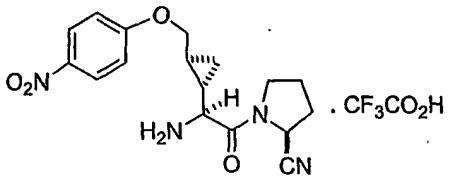
Step 1: 1-{2-(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-flurophenylcarbamoyl) cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carboxamide: Reaction of Intermediate 11 (500 mg, 1.406 mmol) with 4-fluoroaniline (187 mg, 1.687 mmol) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg, 1.687 mmol), 1-hydroxybenzotriazole (228 mg, 1.687 mmol), and triethylamine (285 mg, 2.813 mmol) in dichloromethane (50 ml) gave 135 mg (21 %) of the product as a white hygroscopic solid IR (KBr) 3223, 3020, 1678, 1646, 1509, 1215, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-0.98 (m, 1H), 1.22-1.42 (m, 2H), 1.43, 1.45 (s, 9H), 1.66-1.76 (m, 1H), 1.90-2.20 (m, 4H), 3.67-3.69 (m, 2H), 4.42-4.46 (m, 1H), 4.79 (t, J = 7.8 Hz, 1H), 5.40 (d, J = 6.9 Hz, 1H), 5.61 (br s, 1H), 6.20 (br s, 1H), 6.94-7.00 (m, 2H), 7.50-7.56 (m, 2H), 9.14 (br s, 1H).

Step 2: 1-{2-(2*S*)-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-flurophenylcarbamoyl) cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (130 mg, 0.290 mmol) with $POCl_3$ (0.107 ml, 1.160 mmol)) in pyridine (3 ml) as described in Example 1, Step 1 gave 75 mg (60 %) of the product as a semi-solid; IR (neat) 3325, 3018, 1655, 1509, 1413, 1216, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.05 (m, 1H), 1.25-1.42 (m, 1H), 1.42, 1.44 (s, 9H), 1.63-1.69 (m, 1H), 1.83-1.92 (m, 1H), 2.02-2.87 (m, 4H), 3.67-3.74 (m, 2H), 4.64 (t, *J* = 6.9 Hz, 1H), 4.73-4.76 (m, 1H), 5.52 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.39-7.50 (m, 2H), 8.09 (br s, 1H).

Step 3: Reaction of Step 2 intermediate (70 mg, 0.162 mmol) with TFA (0.350 ml, 4.54 mmol) as described in Example 1, Step 2 gave 37 mg (51 %) of the product as a crystalline hygroscopic solid; IR (KBr) 3338, 3020, 2928, 1667, 1509, 1216, 758 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.26-1.40 (m, 2H), 1.88-2.00 (m, 2H), 2.04-2.20 (m, 2H), 2.26-2.36 (m, 2H), 3.60-3.74 (m, 2H), 4.25 (d, *J* = 9.0 Hz, 1H), 4.72-4.80 (m, 1H), 7.05-7.11 (m, 2H), 7.30-7.36 (m, 2H).

Example 16

1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-nitrophenoxymethyl)cyclopropyl]ethanoyl} pyrrolidin-2-yl-(2*S*)-carbonitrile trifluoroacetae



Step 1: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-nitrophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide: To a stirred solution of Intermediate 13 (400 mg, 1.17 mmol), 4-nitrophenol (163 mg, 1.17 mmol) and triphenyl phosphine (400 mg, 1.52 mmol) in dry THF (5 ml) was added diethyl azodicarboxylate (306 mg, 1.75 mmol) in dry THF (2 ml) drop wise over 30 min. The mixture was refluxed for 15 h with stirring. The solvent was evaporated under reduced pressure and the residue obtained was purified by silica gel column chromatography using 2 % methanol in dichloromethane to give 410 mg (76 %) of the product as a pale yellow solid; IR (KBr) 3419, 2225, 1642, 1510, 1341, 1171 cm^{-1};

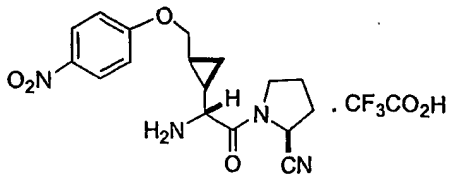
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64-0.70 (m, 1H), 0.81-0.87 (m, 1H), 1.26-1.31 (m, 1H), 1.42, 1.43 (s, 9H), 1.45-1.49 (m, 1H), 1.91-2.12 (m, 3H), 2.23-2.37 (m, 1H), 3.65-3.68 (m, 2H), 3.75 (dd, *J* = 9.9 , 7.8, Hz, 1H), 4.06 (dd, *J* = 6.6, 6.0 Hz, 1H), 4.51 (t, *J* = 7.5 Hz, 1H), 4.56-4.59 (m, 1H), 5.33 (b, 2H), 6.63 (b, 1H), 6.89 (dd, *J* = 7.5, 2.4 Hz, 2H), 8.81 (dd, *J* = 7.2, 2.1 Hz, 2H).

Step 2: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-nitrophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidin-2-yl-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (250 mg, 0.54 mmol) with $POCl_3$ (330 mg, 2.16 mmol) in pyridine (2 ml) as described in Example 1, Step 1 gave 249 mg yellow solid. The crude product was purified by silica gel column chromatography using 0.5 % methanol in dichloromethane as eluent to give 215 mg (90 %) of the product as a pale yellow solid; IR (KBr) 3419, 2929, 1709, 1655, 1513, 1341, 1260, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68-0.75 (m, 1H), 0.85-0.95 (m, 1H), 1.25-1.37 (m, 2H), 1.42 (s, 9H), 2.16-2.29 (m, 4H), 3.67-3.75 (m, 3H), 4.11 (dd, *J* = 10.2, 5.7 Hz, 1H), 4.41 (dd, *J* = 8.1, 6.6 Hz, 1H), 4.76-4.79 (m, 1H), 5.30-5.33 (m, 1H), 6.92 (dd, *J* = 6.9, 2.1 Hz, 2H), 8.91 (dd, *J* = 7.5, 2.1 Hz, 2H).

Step 3: Reaction of Step 2 intermediate (100 mg, 0.22 mmol) with TFA (595 mg, 23.21 mmol) as described in Example 1, Step 2 gave 64 mg (62 %) of the product as a crystalline hygroscopic solid; IR (KBr) 3437, 2961, 2246, 1672, 1512, 1343, 1202 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 0.88-0.94 (m, 1H), 0.97-1.04 (m, 1H), 1.33-1.40 (m, 1H), 1.45-1.54 (m, 1H), 1.84-1.94 (m, 1H), 1.96-2.07 (m, 1H), 2.14-2.26 (m, 2H), 3.51-3.60 (m, 1H), 3.63-3.71 (m, 1H), 3.76 (dd, *J* = 10.5, 8.4 Hz, 1H), 4.25 (dd, *J* = 11.1, 6.0 Hz, 1H), 4.36 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 9.3 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H).

Example 17

1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-nitrophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetae



Step 1: 1-{(2*R*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2-(4-nitrophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide: Reaction of Intermediate 14 (1.0 g, 2.29 mmol) with 4-nitrophenol (407 mg, 2.92 mmol) in the presence of triphenyl phosphine (1.0 g, 3.80 mmol) and diethyl azodicarboxylate (764 mg, 4.39 mmol) afforded 1.0 g (73 %) of the product as an off-white solid; IR (KBr) 3413, 2978, 1644, 1607, 1512, 1341, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71-0.78 (m, 1H), 0.86-0.92 (m, 1H), 1.23-1.32 (m, 2H), 1.42 (s, 9H), 1.99-2.1 (m, 3H), 2.34-2.35 (m, 1H), 3.52-3.55 (m, 1H), 3.70-3.76 (m, 1H), 3.88-3.94 (m, 1H), 4.01 (t, *J* = 7.2 Hz, 1H), 4.11-4.16 (m, 1H), 4.57-4.60 (m, 1H), 5.36 (t, *J* = 6.9 Hz, 2H), 6.9 (d, *J* = 9.3 Hz, 2H), 6.97 (b, 1H), 8.20 (d, *J* = 9.3 Hz, 2H).

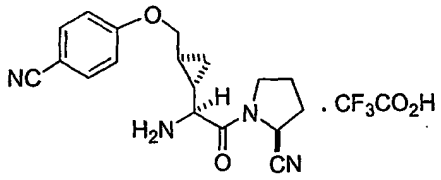
Step 2: 1-{(2*R*)-2-(*tert*-Butoxycarbonyl) amino-2-[(1*R*,2*R*)-2-(4-nitrophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (250 mg, 0.54 mmol) with $POCl_3$ (331 mg, 2.16 mmol) in pyridine (2 ml) as described in Example 1, Step 1 gave 250 mg. The crude product was purified by silica gel column chromatography using 0.5 % methanol in dichloromethane as eluent to give 215 mg (89 %) of the product as a pale yellow solid; IR (KBr) 3411, 2979, 2241, 1710, 1656, 1512, 1341 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67-0.73 (m, 1H), 0.77-0.84 (m, 1H), 1.12-1.15 (m, 1H), 1.23-1.32 (m, 1H), 1.41, 1.44 (s, 9H), 2.11-2.37 (m, 4H), 3.52-3.61 (m, 1H), 3.77-3.90 (m, 2H), 3.98-4.07 (m, 1H), 4.31 (t, *J* = 8.1 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 1H), 5.33-5.40 (m, 1H), 6.87 (d, *J* = 9.3 Hz, 2H), 8.18 (d, *J* = 9.6 Hz, 2H).

Step 3: Reaction of Step 2 intermediate (100 mg, 0.22 mmol) with TFA (595 mg, 5.22 mmol) as described in Example 1, Step 2 gave 67 mg (65 %) of the product as a crystalline hygroscopic solid; IR (KBr) 3373, 2959, 2246, 1673, 1593, 1202 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.92-0.99 (m, 1H), 1.03-1.09 (m, 1H), 1.41-1.45 (m, 2H), 2.09-2.29 (m, 4H), 3.53-3.65 (m, 1H), 3.76-3.82 (m, 1H), 3.84-3.90 (m, 1H), 4.21-

4.29 (m, 2H), 4.75-4.80 (m, 1H), 7.04 (dd, J = 9.3, 1.8 Hz, 2H), 8.2 (dd, J = 9.3, 1.8 Hz, 2H).

Example 18

1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)carbonitrile trifluoroacetae



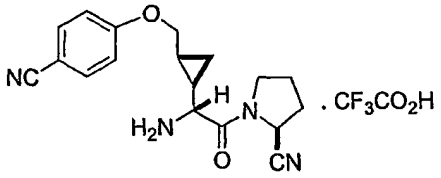
Step 1: 1-{(2*S*)-2-(*tert*-butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2(*S*)-carboxamide: Reaction of Intermediate 13 (400 mg, 1.17 mmol) with 4-cyanophenol (140 mg, 1.17 mmol) in the presence of triphenyl phosphine (400 mg, 1.52 mmol) and diethyl azodicarboxylate (306 mg, 1.75 mmol) afforded 404 mg (78 %) of the product as a white solid; IR (KBr) 3415, 2977, 2225, 1693, 1642, 1605, 1508, 1256, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66-0.68 (m, 1H), 0.79-0.86 (m, 1H), 1.23-1.29 (m, 2H), 1.42, 1.43 (s, 9H), 1.94-2.07 (m, 3H), 2.31- 2.35 (m, 1H), 3.64-369 (m,3H), 4.00 (dd, 10.2, 6.3 Hz, 1H), 4.5 (t, J = 7.5 Hz, 1H), 4.56- 4.59 (m, 1H), 5.30 (br s, 2H), 6.65 (br s, 1H), 6.68 (dd, J = 6.9, 2.1 Hz, 2H), 7.56 (dd, J = 7.2, 1.8 Hz, 2H).

Step 2: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (240 mg, 0.54 mmol) with $POCl_3$ (249 mg, 2.16 mmol) in pyridine (2 ml) as described in Example 1, Step 1, gave 248 mg. The crude product was purified by silica gel column chromatography using 0.5 % methanol in dichloromethane as eluent to give 222 mg (96 %) of the product as a white solid; IR (KBr) 3423, 2979, 2225, 1711, 1656, 1605, 1509, 1427, 1256, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66- 0.73 (m, 1H), 0.83- 0.90 (m, 1H), 1.25- 1.33 (m, 2H), 1.42, 1.44 (s, 9H), 2.13- 2.39 (m, 4H), 3.63- 3.72 (m, 3H), 4.10 (dd, J = 9.9, 5.1 Hz, 1H), 4.43 (dd, J = 8.1, 6.9 Hz, 1H), 4.75-4.78 (m, 1H), 5.30 (d, J = 8.7 Hz, 1H), 6.91 (dd, J = 7.2, 1.8 Hz, 2H), 7.57 (dd, J = 7.2, 1.8 Hz, 2H).

Step 3: Reaction of Step 2 intermediate (100 mg, 0.23 mmol) with TFA (595 mg, 5.22 mmol) as described in Example 1, Step 2 gave 55 mg (53 %) of the product as a white hygroscopic solid; IR (neat) 3411, 2925, 2226, 1672, 1605, 1508, 1451, 1303, 1259, 1174 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.85- 0.92 (m, 1H), 0.95-1.02 (m,1H), 1.30-1.37 (m,1H), 1.43-1.51 (m,1H), 1.78-1.88 (m, 1H), 1.96-2.09 (m, 1H), 2.12-2.25 (m, 2H), 3.48-3.50 (m, 1H), 3.57-3.62 (m, 1H), 3.74 (dd, *J* = 10.8, 8.4 Hz, 1H), 4.24 (dd, *J* = 11.1, 6.0 Hz, 1H), 4.36 (d, *J* = 8.1 Hz, 1H), 4.67-4.71 (m, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H).

Example 19

1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-cyanophenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetae



Step 1: 1-{(2*R*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carboxamide: Reaction of Intermediate 14 (1.0 g, 2.29 mmol) with 4-cyanophenol (349 mg, 2.92 mmol) in the presence of triphenyl phosphine (1.0g, 3.80mmol) and diethyl azodicarboxylate (764mg, 4.39mmol) afforded 1.01 g (77 %) of the product as a white solid; IR (KBr) 3418, 2978, 2225, 1645, 1508, 1256, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.69-0.76 (m, 1H), 0.84-0.91 (m, 1H), 1.26-1.34 (m, 2H), 1.42 (s, 9H), 1.99-2.09 (m, 3H), 2.34-2.38 (m, 1H), 3.51-3.54 (m, 1H), 3.66 (dd, *J* = 9.9, 7.5 Hz, 1H), 3.87-3.91 (m, 1H), 4.01-4.03 (m, 1H), 4.10 (dd, *J* = 9.9, 5.1 Hz, 1H), 4.58-4.60 (m,1H), 5.33 (br t, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.97 (br s, 1H), 7.57 (d, *J* = 6.9 Hz, 2H).

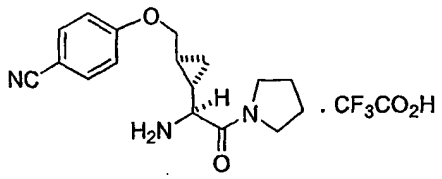
Step 2: 1-{(2*R*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*R*,2*R*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile: Reaction of Step 1 intermediate (400 mg, 0.90 mmol) with $POCl_3$ (553 mg, 3.61 mmol) in

pyridine (2 ml) as described in Example 1, Step 1 gave 364 mg (94 %) of the product as a white solid; IR (KBr) 3330, 2979, 2225, 1709, 1656, 1508, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.65-0.69 (m, 1H), 0.71-0.80 (m, 1H), 1.25-1.38 (m, 2H), 1.41, 1.44 (s, 9H), 2.11-2.34 (m, 4H), 3.52-3.61 (m, 1H), 3.73 (dd, J = 10.2, 7.2 Hz, 1H), 3.81-3.86 (m, 1H), 3.93- 4.01 (m, 1H), 4.29 (t, J = 7.5 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 5.30-5.39 (m, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H).

Step 3: Reaction of Step 2 intermediate (150 mg, 0.35 mmol) with TFA (595 mg, 5.22 mmol) as described in Example 1, Step 2 gave 102 mg (65 %) of the product as a white hygroscopic solid; IR (KBr) 3441, 2226, 1675, 1606, 1509, 1203 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.85-0.92 (m, 1H), 0.95-1.02 (m, 1H), 1.35-1.41 (m, 2H), 1.99-2.27 (m, 4H), 3.48-3.57 (m, 1H), 3.68-3.80 (m, 2H), 4.16 (dd, J = 10.5, 5.4 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.66-4.71 (m, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 9 Hz, 2H).

Example 20

1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine trifluoroacetate



Step 1: (1*S*,2*S*)-2-[(1*S*)-1-(*tert*-Butoxycarbonyl)amino-2-(pyrrolidine-1-yl)-2-oxoethyl] cyclopropane-1-carboxylic acid: To a solution of Intermediate 16 (946 mg, 2.90 mmol) in 20 % aqueous THF (20 ml) was added lithium hydroxide monohydrate (365 mg, 8.70 mmol) and the mixture was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the reaction mixture was diluted with water (100 ml). The basic aqueous solution was washed with ethyl acetate (2 x 25 ml) and then acidified to pH with 1*N* HCl. The acidic aqueous solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford 900 mg (99 %) of the product as a white solid; IR (KBr) 3420, 3312, 2978, 2623, 2355, 1708, 1634, 1512, 1453, 1393, 1342, 1252, 1167, 1024

857, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.06 (m, 1H), 1.21-1.27 (m, 1H), 1.42 (s, 9H), 1.67-1.80 (m, 2H), 1.81-2.01 (m, 4H), 3.45-3.68 (m, 4H), 4.42-4.47 (dd, J = 8.7, 6.3 Hz, 1H), 5.60 (d, J = 8.4Hz, 1H).

Step 2: (2S)-2-(*tert*-Butoxycarbonyl)amino-1-(pyrrolidine-1-yl)-2-[(1S,2S)-2-hydroxy methylcyclopropyl]ethan-1-one: Ethyl chloroformate (402 mg, 2.72 mmol) was added to a stirred solution of step 1 Intermediate (850 mg, 2.72 mmol) and triethylamine (275 mg, 2.72 mmol) in THF (15 ml) at 0 °C. The reaction mixture was further stirred at the same temperature for 30 min. The reaction mixture was filtered to remove triethylamine hydrochloride and the filtrate containing the mixed anhydride was added drop wise to a stirred solution of $NaBH_4$ (308 mg, 8.15 mmol) in 20 % aqueous THF (15 ml) at 10 °C. The mixture was further stirred at same temperature for 1.0 h and further acidified to

pH 4 with saturated NH_4Cl solution at 0 °C. THF was evaporated under reduced pressure and the residue was diluted with water (50 ml). The aqueous solution was further extracted with dichloromethane (3 x 100 ml) and the combined organic extracts were washed with brine (50 ml), dried ($NaSO_4$).The solvent was evaporated under reduced pressure and the residue obtained was purified by silica gel column chromatography using 3 % methanol in dichloromethane to afford 750 mg (93 %) of the product as a white solid; IR (Neat) 3418, 2976, 2932, 2878, 1704, 1632, 1501, 1452, 1392, 1366, 1250, 1168, 1059, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.47-0.53 (m, 1H), 0.62-.069 (m, 1H), 1.07- 1.17 (m, 2H), 1.42 (s, 9H), 1.83-1.99 (m, 4H), 3.23-3.29 (m, 1H), 3.41-3.67 (m, 5H), 4.32 (br s, 1H), 5.09 (br s, 1H).

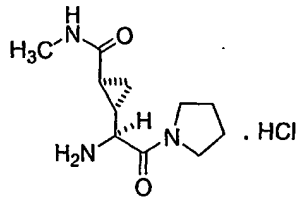
Step 3: 1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine: Reaction of step 2 Intermediate (200 mg, 0.67 mmol) with 4-cyanophenol (80 mg, 0.67 mmol) in the presence of triphenylphosphine (228 mg, 0.87 mmol) and diethyl azodicarboxylate (175 mg, 1.00 mmol) afforded 44 mg (16 %) of the product as a white semisolid; IR (neat) 2976, 2224, 1707, 1642, 1255, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.61-0.67 (m, 1H), 0.79-0.85 (m, 1H), 1.22-1.30 (m, 2H), 1.42 (s, 9H), 1.84-1.99 (m, 4H), 3.38-3.63 (m, 4H), 3.72 (dd, J = 9.9, 6.9 Hz, 1H), 3.96 (dd, J = 9.9, 5.7 Hz, 1H), 4.40

(t, J = 6.9 Hz, 1H), 5.44 (d, J = 7.8 Hz, 1H), 6.87 (dd, J = 9.0, 2.1 Hz, 2H), 7.56 (dd, J = 8.7, 2.1 Hz, 2H).

Step 4: Reaction of Step 3 intermediate (40 mg, 0.10 mmol) with TFA (268 mg, 23.47 mmol) as described in Example 1, Step 2 gave 18 mg (43 %) of the product as a white hygroscopic solid; IR (KBr) 3438, 2979, 2221, 1670, 1605, 1509, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.02 (m, 1H), 1.11-1.14 (m, 1H), 1.52-1.54 (m, 2H), 1.94-2.03 (m, 4H), 3.52-3.62 (m, 4H), 3.97 (t, J = 10.5Hz, 1H), 4.34-4.43 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H).

Example 21

N1-Methyl-(1S,2S)-2-[(1S)1-amino-2-(pyrrolidin-1-yl)-2-oxoethyl]cyclopropane-1-carboxamide hydrochloride



Step 1: N1-Methyl-(1S,2S)-2-[(1S)-1-*tert*-butyloxycarbonylamino-2-(pyrrolidine-1-yl)- 2-oxoethyl]cyclopropane-1-carboxamide: 40 % aqueous methylamine solution (3 ml) was added to a solution of Intermediate 16 (0.275 g, 0.843 mmol) in THF (5 ml). The reaction mixture was stirred at RT for 15 h. The solvent was evaporated under reduced

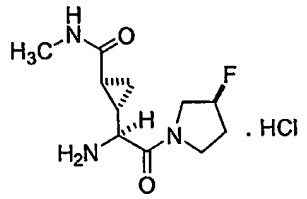
pressure and the residue was purified by silica gel column chromatography using 2 % methanol in dichloromethane to afford 0.276 g (100 %) of the product as a greenish-yellow solid; IR (KBr) 3337, 2976, 2929, 1709, 1643, 1562, 1453, 1366, 1250, 1167, 1049, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.90 (m, 1H), 1.16-1.26 (m, 1H), 1.42 (s, 9H), 1.43-1.52 (m, 1H), 1.60-1.69 (m, 1H), 1.82-2.02 (m, 4H), 2.79 (d, J = 4.8 Hz, 3H), 3.36-3.65 (m, 4H), 4.45 (dd, J = 7.5, 5.1 Hz, 1H), 5.42 (d, J = 8.1 Hz, 1H), 5.69 (br s, 1H).

Step 2: Dry HCl gas was bubbled into a solution of Step 1 intermediate (0.075 g, 0.23 mmol) in CH_2Cl_2 (3 ml) at 0 °C. After the solution was saturated, HCl purging was

discontinued and the reaction mixture was stirred at 0 °C for 15 min. Excess HCl gas and CH_2Cl_2 were evaporated under reduced pressure and the syrupy residue obtained was triturated with diethyl ether (5 ml) to give 45 mg (75 %) of the product as an off-white solid; IR (KBr) 3429, 2926, 1643, 1457, 1409, 1162, 1061, 1021, 940, 866 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.08-1.22 (m, 2H), 1.65-1.78 (m, 2H), 1.80-2.00 (m, 4H), 2.67 (s, 3H), 3.35-3.58 (m, 4H), 4.12 (d, J = 8.4 Hz, 1H).

Example 22

***N*1-Methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(3*S*)-3-fluoropyrrolidin-1-yl]-2-oxoethyl}-cyclopropane-1-carboxamide hydrochloride**

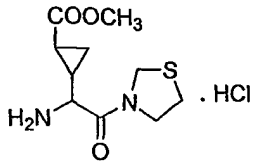


Step 1: *N*1-Methyl-(1*S*,2*S*)-2-{(1*S*)-1-(*tert*-butoxycarbonyl)amino-2-[(3*S*)-3-fluoro-pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide: Coupling reaction of Intermediate 15 (200 mg, 0.73 mmol), with Intermediate 17 (230 mg, 0.88 mmol) using pivaloyl chloride (97 mg, 0.80 mmol) and *N*-methylmorpholine (223 mg, 2.20 mmol) as described in Intermediate 19, gave 220 mg (87 %) of the product as an off-white solid; IR (KBr) 3328, 2980, 1702, 1645, 1453, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.89 (m, 1H), 1.17-1.25 (m, 1H), 1.34-1.54 (m, 1H), 1.43 (s, 9H), 1.59-1.78 (m, 1H), 1.86-2.44 (m, 2H), 2.79, 2.80 (2d, J = 3.9, 3.6 Hz, 3H), 3.4-4.01 (m, 4H), 4.46 (m, 1H), 5.17-5.44 (m, 2H), 5.7 (br s, 1H).

Step 2: Deprotection of Step 1 intermediate (70 mg, 0.20 mmol) as described in Example 19, step 2, gave 49 mg (85 %) of the product as a white hygroscopic solid; IR (KBr) 2922, 2851, 1744, 1401, 1161 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.30-1.37 (m, 2H), 1.92-1.97 (m, 2H), 2.33-2.52 (m, 2H), 2.86 (s, 3H), 3.66-4.01 (m, 4H), 4.35-4.43 (m, 1H), 5.45-5.63 (m, 1H).

Example 23

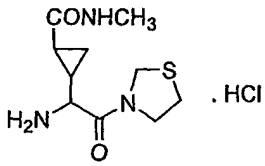
Methyl(1*RS*,2*RS*)-2-((1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl)cyclopropane -1-carboxylate hydrochloride



Dry HCl gas was bubbled into a solution of intermediate 19 (100 mg, 0.29 mmol) in dichloromethane (5 ml) at 0 °C for 5 min. The solution was stirred for 30 min at the same temperature. The solvent was evaporated under reduced pressure and the residue obtained was triturated with dry diethyl ether to give 69.33 mg (85 %) of the product as a white hygroscopic solid; IR(KBr)3429,2999,1716,1668,1439,1219 cm^{-1} ; ^1H NMR (300 MHz, D_2O) δ 1.18-1.40 (m, 2H), 1.82-1.89 (m, 2H), 3.04-3.13 (m, 2H), 3.65 (s,3H),3.72-3.86 (m, 2H), 4.15-4.28 (m, 1H), 4. 47-4.59 (m, 2H).

Example 24

***N*1-Methyl-(1*RS*,2*RS*)-2-[(1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cycloprop- ane-1-carboxamide hydrochloride**

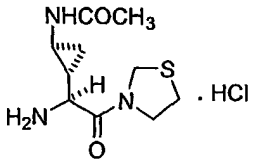


Step1: *N*1-methyl-(1*RS*,2*RS*)-2-[(1*RS*)-1-(*tert*-butoxycarbonyl)amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cyclopropane-1-carboxamide: To a stirred solution of Intermediate 19 (240 mg, 0.70 mmol) in THF (5 ml) was added a 40 % aqueous solution of methyl amine (5 ml) at room temperature. Stirring was continued overnight. THF and water were removed under reduced pressure to afford the product as a yellow solid (235 mg, 98 %). IR (KBr) 3345, 2929, 1691, 1645, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.88 (m, 1H), 1.19-1.25 (m, 1H), 1.43 (s, 9H), 1.66-1.68 (m, 1H), 1.99 -2.01 (m, 2H), 2.81 (s, 3H) 3.02-3.14 (m, 2H), 3.78-3.92 (m, 2H), 4.44-4.68 (m, 2H), 4.64-4.67 (m, 1H), 5.38-5.41 (d, J = 9.0 Hz, 1H), 5.72 (br s, 1H).

Step 2: Dry HCl gas was bubbled into a solution of Step 1 intermediate (100 mg, 0.29 mmol) in dichloromethane (5 ml) for 5 min at 0 °C. The solution was stirred for 30 min at the same temperature. The solvent was evaporated under reduced pressure and the residue obtained was triturated with dry diethyl ether to give 64.39 mg (79 %) of the product as a white solid. IR (KBr) 3369, 2924, 1649, 1215 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.12-1.23 (m, 2H), 1.71-1.76 (m, 2H), 2.67 (s, 3H), 3.04-3.12 (m, 2H), 3.71-3.84 (m, 2H), 4.19-4.28 (m, 1H), 4.47-4.58 (m, 2H).

Example 25

***N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cyclopropane-1-carboxamide hydrochloride**



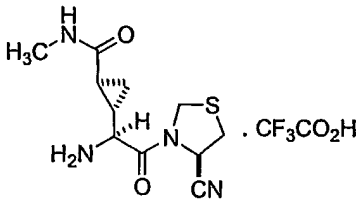
Step 1: *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-(*tert*-butoxycarbonyl)amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cyclopropane-1-carboxamide: Pivaloyl chloride (68 mg, 0.565 mmol) was added to a stirred and cooled (0 °C) solution of Intermediate 15 (140 mg, 0.514 mmol) and *N*-methylmorpholine (78 mg, 0.77 mmol) in dry THF (4 ml) to result a white precipitate. The mixture was further stirred at the same temperature for 30 min. Thiazolidine (60 mg, 0.66 mmol) in THF (1.0 ml) was added and the mixture was further stirred for 2 h at the same temperature. The reaction mixture was diluted with THF (10 ml), filtered and the filtrate was concentrated to give a viscous residue. The residue was purified by silica gel column chromatography using 3 % methanol in dichloromethane to give 130 mg (73 %) of the product as a white solid; IR (KBr) 3345, 2929, 1691, 1645, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-0.88 (m, 1H), 1.18-1.28 (m, 2H), 1.43 (s, 9H), 1.63-1.69 (m, 1H), 2.79 (d, J = 4.8 Hz, 3H), 3.03 (t, J = 5.4 Hz, 1H), 3.11 (t, J = 6.3 Hz, 1H), 3.787-3.84 (m, 1H), 3.86-3.90 (m, 1H), 4.44-4.57 (m, 2H), 4.64-4.67 (m, 1H), 5.29 (br s, 1H), 5.70 (br s, 1H).

Step 2: Dry HCl gas was bubbled into a solution of Step 1 intermediate (50 mg, 0.14 mmol) in dichloromethane (4 ml) for 5 min. The solution was stirred for 30 min at the same temperature. The solvent was evaporated under reduced pressure and the residue

obtained was triturated with dry diethyl ether to give 32 mg (78 %) of the product as a white hygroscopic solid; IR (neat) 3369, 2928, 1649, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.1-1.23 (m, 2H), 1.71-1.76 (m, 2H), 2.67 (s, 3H), 3.04-3.12 (m, 2H), 3.73-3.84 (m, 2H), 4.19-4.28 (m, 1H), 4.50-4.58 (m, 2H).

Example 26

N1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(4-(4*S*)-cyano-1,3-thiazolan-3-yl)ethyl]-cyclopropane-1-carboxamide trifluoroacetate



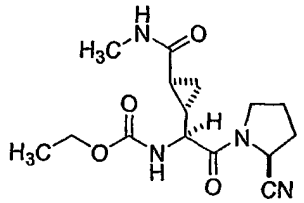
Step 1: (4*S*)-3-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-methylcarbomoyl-cyclopropyl]ethanoyl}-1,3-thiazolane-4-carboxamide: Coupling reaction of Intermediate 18 (335 mg, 1.10 mmol) with Intermediate 15 (200 mg, 0.73 mmol) using pivaloyl chloride (97 mg, 0.80 mmol) and *N*-methylmorpholine (222 mg, 2.2 mmol) as described in Example 19, Step 1 gave 160 mg (56 %) of the product as a white solid; IR (KBr) 3333, 1684, 1517, 1442, 1366, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.92 (m, 1H), 1.19-1.25 (m, 1H), 1.43 (s, 9H), 1.59-1.65 (m, 1H), 1.75-1.79 (m, 1H), 2.79 (d, J = 4.8 Hz, 3H), 3.2-3.26 (m, 1H), 3.34-3.4 (m, 1H), 4.58-4.61 (m, 2H), 4.8 (d, J = 8.7 Hz, 1H), 4.95-4.98 (m, 1H), 5.36 (d, J = 7.5 Hz, 1H), 5.52 (br s, 1H), 6.2 (br s, 1H), 6.32 (br s, 1H).

Step 2: *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-(*tert*-butoxycarbonyl)amino-2-oxo -2-(4-(4*S*)-cyno-1, 3-thiazolan-3-yl) ethyl] cyclopropane-1-carbonitrile: Reaction of Step 1 intermediate (145 mg, 0.37 mmol) with $POCl_3$ (230 mg, 1.50 mmol) in pyridine (2 ml) as described in Example 1, Step 1 gave 125 mg (90 %) of the product as an off-white solid; IR (KBr) 3341, 2980, 2246, 1687, 1524, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92-0.95 (m, 1H), 1.25-1.31 (m, 1H), 1.43 (s, 9H), 1.80-1.82 (m, 2H), 2.79 (d, J = 4.8 Hz, 3H), 3.30-3.32 (m, 2H), 5.58 (t, J = 7.2 Hz, 1H), 4.64 (d, J = 8.4 Hz, 1H), 4.77 (d, J = 8.7 Hz, 1H), 5.23-5.25 (m, 2H), 5.80 (br s, 1H).

Step 3: Reaction of Step 2 intermediate (125 mg, 0.33 mmol) with TFA (521 mg, 13.47 mmol) as described in Example 1, Step 2 gave 80 mg (61 %) of the product as a white hygroscopic solid; IR (KBr) 3413, 2924, 1685, 1559, 1524, 1436, 1319, 1128 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.15-1.19 (m, 1H), 1.22-1.3 (m, 1H), 1.71-1.77 (m, 1H), 1.8-1.89 (m, 1H), 2.68 (s, 3H), 3.4-3.42 (m, 2H), 4.30 (d, J = 8.4 Hz, 1H), 4.66-4.77 (m, 2H), 5.25 (t, J = 4.8 Hz, 1H).

Example 27

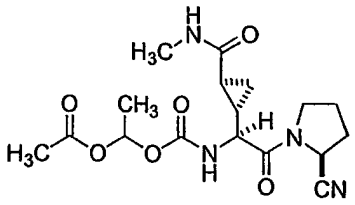
N1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-ethoxycarbonylamino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxaamide



Ethyl chloroformate (0.10 g, 0.92 mmol) and pyridine (0.18 g, 2.30 mmol) were added to a cooled suspension of N1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide hydrochloride (0.22 g, 0.768 mmol) in CH_2Cl_2 at 0 °C. To the stirred mixture, pyridine (0.18 g, 2.30 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C. It was then diluted with CH_2Cl_2 (20 ml) and washed successively with 1N HCl solution, water, saturated $NaHCO_3$ solution and brine. The dichloromethane layer was dried (Na_2SO_4) and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography using 2 % methanol in dichloromethane as an eluent to afford 0.18 g (73 %) of the product as an off-white solid; mp 70-72 °C; IR (KBr) 3337, 2961, 2934, 2244, 1708, 1683, 1650, 1534, 1424, 1250, 1187, 1070 901, 779 649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-0.96 (m, 1H), 1.22-1.33 (m, 4H), 1.38-1.45 (m, 1H), 1.75-1.82 (m, 1H), 2.12-2.35 (m, 4H), 2.80 (d, J = 4.8 Hz, 3H), 3.62-3.78 (m, 2H), 4.05 (q, J = 6.9 Hz, 2H), 4.60 (dd, J = 7.8, 6.3 Hz, 1H), 4.73-4.77 (m, 1H), 5.48 (d, J = 7.5 Hz, 1H), 5.77 (b, 1H).

Example 28

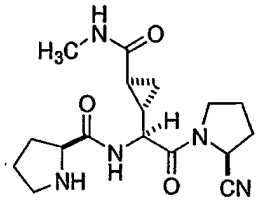
N1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-acetoxyethoxycarbonylamino-2-[(2*S*)-2-cyanopyrrolin-1-yl]-2-oxoethyl}cyclopropane-1-carboxaamide



Pyridine (0.074 g, 0.93 mmol) was added to a suspension of *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanoazolan-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide hydrochloride (0.10 g, 0.335mmol) and α-acetoxyethyl *p*-nitrophenyl carbonate (0.103 g, 0.38 mmol), prepared according to Alexander et al., *J. Med. Chem.* **1988**, *31*, 318, in CH_2Cl_2 (5 ml). To this reaction mixture, DMAP (0.002 g, 0.017 mmol) was added and the reaction mixture was stirred at RT for 5 days. The solvent was removed under reduced pressure and the residue obtained was purified by silica gel column chromatography using 2 % methanol in CH_2Cl_2 as eluent to afford 0.08 g (60 %) of the product as a white solid; IR (KBr) 2959, 2925, 2244, 1739, 1651, 1548, 1436, 1260, 1081, 1021, 1012, 945, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-0.94 (m, 1H), 0.96-1.02 (m, 1H), 1.45 (d, *J* = 5.4 Hz, 3H), 1.56-1.94 (m, 2H), 2.10 (s, 3H), 2.15-2.32 (m, 4H), 2.79 (d, *J* = 4.8 Hz, 3H), 3.59-3.79 (m, 2H), 4.35 (t, *J* = 7.8 Hz, 1H), 4.72-4.76 (m, 1H), 5.65 (br s, 1H), 6.19 (br s, 1H), 6.78 (m, 1H).

Example 29

N1-methyl-(1S,2S)-2-{(1S)-1-[(2S)pyrrolidin-2-ylcarboxamido]-2-[(2S)-2-cyano pyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide trifluoroacetate



Step 1: *N*1-methyl-2-{1-[(2*S*)-1-*tert*-butoxycarbonylazolan-2-ylcarboxamido]-2-[(2*S*)-2-cyanoazolan-1-yl]-2-oxoethyl}-1-cyclopropanecarboxamide: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.16 g, 0.86 mmol) was added to a stirred suspension of N-BOC-L-proline (0.15 g, 0.71 mmol) and 1-hydroxybenzotriazole (0.13 g, 0.86 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The reaction

mixture was stirred for 1 h at 0 °C to obtain a clear solution. To it, was added *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanoazolan-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide hydrochloride (0.24 g, 0.86 mmol) followed by addition of pyridine (0.15 g, 1.92 mmol). The reaction mixture was allowed to warm to RT and stirred for 20 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed successively with 1N HCl, water, aqueous $NaHCO_3$ solution and brine and dried (Na_2SO_4) The solvent was evaporated under reduced pressure and the residue obtained was purified silica gel column chromatography using 1 % methanol in dichloromethane as eluent to yield 0.31 g (82 %) of the product as an off-white solid; IR (KBr) 3362, 2977, 2361, 1650, 1544, 1411, 1367, 1244, 1163, 1127, 773 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.78-0.91 (m, 2H), 1.32, 1.39 (s, 9H), 1.45-1.80 (m, 5H), 1.90-2.22 (m, 5H), 2.55-2.59 (m, 3H), 3.20-3.38 (m, 2H), 3.48-3.68 (m, 2H), 4.09-4.25 (m, 2H), 4.65-4.75 (m, 1H), 7.90-7.97 (m, 1H), 8.41 (d, J = 7.2 Hz, 1H)

Step 2: Reaction of Step 1 intermediate (100 mg, 0.22 mmol) with TFA (1.5 ml) in dichloromethane (1.5 ml) at 0 °C as described in Example 1, Step 2 gave 50 mg of the product as a white hygroscopic solid; ^1H NMR (300 MHz, D_2O) δ 0.89-0.96 (m, 1H), 1.01-1.08 (m, 1H), 1.47-1.53 (m, 1H), 1.55-1.65 (m, 1H), 1.80-2.35 (m, 8H), 2.56 (s, 3H), 3.15-3.30 (m, 2H), 3.51-3.61 (m, 2H), 4.23-4.28 (m, 2H), 4.56-4.60 (m, 1H).

PROTOCOL FOR THE DPP-IV ASSAY

DPP-IV inhibition measurement in vitro: DPP-IV activity was determined by the cleavage rate of 7-amino-4-methyl coumarin (AMC) from synthetic substrate Glycyl-Prolyl-AMC. In brief, the assay was conducted by adding 10 ng of human recombinant Dipeptidyl peptidase IV enzyme (DPPIV, available commercially from R & D Systems) in 50 µl of the assay buffer (25 mM Tris, pH 7.4, 140 mM NaCl, 10 mM KCl, 1% BSA) to 96 well black flat bottom microtiter plates. The reaction was initiated by adding 50 µl of 100 µM substrate Gly-Pro-AMC. The incubation was carried out in the kinetic mode at 30°C for 30 minutes. Fluorescence was measured using Fluorostar at excitation filter of 380 nm and emission filter of 460 nm) Test compounds and solvent controls were added as 1 µl additions. A standard curve of free amino methyl coumarin (AMC) was generated using 0-100 µM AMC in the

assay buffer. The curve generated, which was linear was used for the interpolation of catalytic activity.

TESTS FOR IC_{50} STUDIES:

Test compounds dissolved in DMSO at 5-6 concentrations were tested in duplicate along with the solvent control and blank samples. Percent inhibition was calculated at each concentration with respect to the solvent control sample (no test compound added). IC_{50} values were calculated from 3 experiments using the prism software.

Compound	IC_{50} (nM)
Example-1	68.80
Example-2	>300
Example-3	140.8
Example-4	126
Example-5	11 % at 300 nM
Example-6	10.78
Example-7	2.49
Example-8	0 % at 300 nM
Example-9	19.24
Example-10	2.59
Example- 11	47 % at 300 nM
Example-12	7.14
Example-13	18.89
Example-14	57.5
Example-15	10.82
Example-16	4.33
Example-17	4 % at 300 nM
Example-18	3.47
Example-19	29 % at 300 nM
Example-20	23 % at 300 nM
Example-21	17 % at 300 nM
Example-22	13 % at 300 nM
Example-23	3 % at 300 nM
Example-24	0 % at 300 nM
Example-25	17% at 300 nM
Example-26	6.46

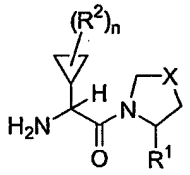
Example-27	4% at 300 nM
Example-29	0% at 300 nM

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

All patent and non-patent publication cited in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS:

1. A compound of general Formula (I)



(I)

wherein:

X is selected from -S (O)$_m$, -CH_2-, CHF, and -CF_2;

m is 0, 1 or 2;

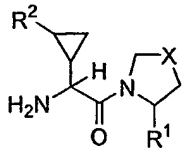
n is 0, 1 , 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, examples of isosters of carboxylic acids include but are not limited to SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, -$COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, -NR^3COR^4,NR^3COOR^4, $NR^3S(O)_mR^4$, -$S(O)_mNR^3R^4$, -$OCONR^3R^4$,- OR^3 ,-R^3 ,-SR^3;

R^3 and R^4 may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 of the general Formula (II)



(II)

wherein:

X is selected from -S (O) $_m$, -CH_2-, CHF, and -CF_2;

m is 0, 1 or 2;

n is 0, 1 , 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, examples of isosters of carboxylic acids include but are not limited to SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, -$COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, -NR^3COR^4,NR^3COOR^4, $NR^3S(O)_mR^4$, -$S(O)_mNR^3R^4$, -$OCONR^3R^4$,- OR^3 ,-R^3 ,-SR^3;

R^3 and R^4 may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 or 2 ,wherein the substituents in the 'substituted alkyl', 'substituted alkoxy', 'substituted alkenyl', 'substituted alkynyl', 'substituted cycloalkyl', 'substituted cycloalkylalkyl', 'substituted cycloalkenyl', 'substituted arylalkyl', 'substituted aryl', 'substituted heterocyclic ring', 'substituted heteroaryl ring', 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring', 'substituted amino', 'substituted alkoxycarbonyl', 'substituted cyclic ring', 'substituted alkylcarbonyl', 'substituted alkylcarbonyloxy' and 'substituted carboxylic acid' may be the same or different, which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), or optionally substituted groups selected from alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclic ring, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yR^z$, $-R^xR^yR^z$, $-R^xCF_3$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroarylalkyl.

4. A compound according to claim 1, wherein X is $-CH_2-$.

5. A compound according to claim 1, wherein X is –CHF-.

6. A compound according to claim 1, wherein X is $-S(O)_m-$ and m is 0.

7. A compound according to claim 1, wherein R^1 is Hydrogen.

8. A compound according to claim 1, wherein R^1 is nitrile (-CN).

9. A compound according to claim 1, wherein R^1 is $-CONH_2$.

10. A compound according to claim 1, wherein R^2 is cyano(-CN).

11 A compound according to claim 1, wherein R^2 is COR^3.

12. A compound according to claim 1, wherein R^2 is $COOR^3$.

13. A compound according to claim 1, wherein R^2 is CH_2OR^3 .

14. A compound according to claim 1, wherein R^2 is $CONR^3R^4$.

15. A compound according to claim 1, wherein R^3 is Hydrogen.

16. A compound according to claim 1, wherein R^3 is Methyl.

17. A compound according to claim 1, wherein R^3 is Pyrrolidin-1yl.

18. A compound according to claim 1, wherein R^3 is 4-Nitro phenyl.

19. A compound according to claim 1, wherein R^3 is 4-Cyano phenyl.

20. A compound according to claim 1, wherein R^4 is methyl.

21. A compound according to claim 1, wherein R^4 is ethyl.

22. A compound according to claim 1, wherein R^4 is isopropyl.

23. A compound according to claim 1, wherein R^4 is n-hexyl.

24. A compound according to claim 1, wherein R^4 is n-butyl.

25. A compound according to claim 1, wherein R^4 is 4-flurophenyl.

26. A compound according to claim 1, Methyl (1*RS*,2*RS*)-2-{(1*RS*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate and pharmaceutically acceptable salts thereof.

27. A compound according to claim 1,Methyl (1*S*, 2*S*)-2-{(1*S*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxylate trifluoroacetate and pharmaceutically acceptable salts thereof.

28. A compound according to claim 1,Methyl(1*R*,2*R*)-2-{(1*R*)-1-amino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl} ycloropane-1-carboxylate trifluoroacetate and pharmaceutically acceptable salts thereof.

29. A compound according to claim 1,1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-cyanocyclo -propyl]ethanoyl}pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

30. A compound according to claim 1,1-{(2*S*)-amino-2-[(1*S*,2*S*)-2-methyl carbamoylcyclopropyl]ethanoyl} pyrrolidine-2-(2*S*)-carboxamide trifluoroacetate and pharmaceutically acceptable salts thereof.

31. A compound according to claim 1,1-{2(*S*)-2-Amino-2-[(1S,2S)-2-methyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

32. A compound according to claim 1,1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-methyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile hydrochloride and pharmaceutically acceptable salts thereof.

33. A compound according to claim 1,1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-methyl carbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile hydrochloride and pharmaceutically acceptable salts thereof.

34. A compound according to claim 1,1-{(2S)-2-Amino-2-[(1S,2S)-2-ethyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2S)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

35. A compound according to claim 1,1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-isopropyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

36. A compound according to claim 1,1-{2(*R*)-2-Amino-2-[(1*R*,2*R*)-2-isopropyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2(S)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

37. A compound according to claim 1,1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-butyl carbamoylcyclopropyl]acetyl}pyrrolidine-2(*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

38. A compound according to claim 1,1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-hexyl carbamoylcyclopropyl]acetyl}-pyrrolidine-2(*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

39. A compound according to claim 1,1-{2(*S*)-2-Amino-2-[(1*S*,2*S*)-2-azolanyl carbamoylcyclopropyl]acetyl} pyrrolidine-2(*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

40. A compound according to claim1,1-{2-(2*S*)-Amino-2-[(1*S*,2*S*)-2-(4-fluoro phenylcarbamoyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

41. A compound according to claim1,1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-nitro phenolxymethyl)cyclopropyl]ethanoyl}pyrrolidin-2-yl-(2*S*)-carbonitrile trifluoroacetate and pharmaceutically acceptable salts thereof.

42. A compound according to claim 1,1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-nitro phenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetae and pharmaceutically acceptable salts thereof.

43. A compound according to claim 1,1-{(2*S*)-2-Amino-2-[(1*S*,2*S*)-2-(4-cyano phenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)carbonitrile trifluoroacetae and pharmaceutically acceptable salts thereof.

44. A compound according to claim 1,1-{(2*R*)-2-Amino-2-[(1*R*,2*R*)-2-(4-cyano phenoxymethyl)cyclopropyl]ethanoyl}-pyrrolidine-2-(2*S*)-carbonitrile trifluoroacetae and pharmaceutically acceptable salts thereof.

45. A compound according to claim 1,1-{(2*S*)-2-(*tert*-Butoxycarbonyl)amino-2-[(1*S*,2*S*)-2-(4-cyanophenoxymethyl)-cyclopropyl]ethanoyl}pyrrolidine trifluoroacetate and pharmaceutically acceptable salts thereof.

46. A compound according to claim 1,*N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)1-amino-2-(pyrrolidin-1-yl)-2-oxoethyl]cyclo- propane -1-carboxamide hydrochloride and pharmaceutically acceptable salts thereof.

47. A compound according to claim 1,*N*1-Methyl-(1*S*,2*S*)-2-{(1*S*)-1-amino-2-[(3*S*)-3-fluoropyrrolidin-1-yl]-2-oxoethyl}-cyclopropane-1-carboxamide hydrochloride and pharmaceutically acceptable salts thereof.

48. A compound according to claim 1, Methyl(1*RS*,2*RS*)-2-((1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl)cyclo- propane-1-carboxylate hydrochloride and pharmaceutically acceptable salts thereof.

49. A compound according to claim 1, *N*1-Methyl-(1*RS*,2*RS*)-2-[(1*RS*)-1-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl] cyclopropane-1-carboxamide hydrochloride and pharmaceutically acceptable salts thereof.

50. A compound according to claim 1, *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(1,3-thiazolan-3-yl)ethyl]cyclo- propane-1-carboxamide hydrochloride and pharmaceutically acceptable salts thereof.

51. A compound according to claim 1, *N*1-Methyl-(1*S*,2*S*)-2-[(1*S*)-amino-2-oxo-2-(4-(4*S*)-cyano-1,3-thiazolan-3-yl)ethyl]cyclopropane-1-carboxamide trifluoroacetate and pharmaceutically acceptable salts thereof.

52. A compound, *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-ethoxy carbonylamino-2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide and pharmaceutically acceptable salts thereof.

53. A compound, *N*1-methyl-(1*S*,2*S*)-2-{(1*S*)-1-acetoxy ethoxycarbonylamino-2-[(2*S*)-2-cyanopyrrolin-1-yl]-2-oxoethyl}cyclopropane-1-carbox- amide and pharmaceutically acceptable salts thereof.

54. A compound, *N*1-methyl-(1S,2S)-2-{(1S)-1-[(2S)pyrrolidin-2-ylcarboxamido] -2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}cyclopropane-1-carboxamide trifluoroacetate and pharmaceutically acceptable salts thereof.

55. A pharmaceutical composition comprising a compound according to any one of claims 1-53 or 54.

56. A pharmaceutical composition useful in the treatment and/or prophylaxis of diseases, which are associated with DPP-IV, the composition comprising, as an

active ingredient, a compound according to claims 1 to 53 or 54 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

57. A method for the treatment and/or prophylaxis of diseases which are associated with DPP-IV, selected from the group consisting of diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, ulcerative colitis, Crohns disease, obesity, and metabolic syndrome, which method comprises administering to a host suffering therefrom a therapeutically effective amount of a compound according to claims 1 to 53 or 54.

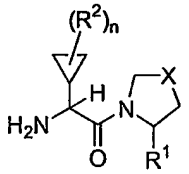
58. The method of claim 55, wherein the compound is administered in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

59. A method of treating insulin resistant non-impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to claims 1 to 53 or 54.

60. A pharmaceutical composition comprising, as an active ingredient, a compound according to claims 1-53 or 54 or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

61. A method for the manufacture of a medicament or a pharmaceutical composition comprising admixing a compound according to claims 1 to 53 or 54, and a pharmaceutically acceptable carrier or excipient.

62. A process for the preparation of compounds of the general formula (I):



(I)

wherein:

X is selected from -S (O) $_m$, -CH_2-, CHF, and -CF_2;

m is 0, 1 or 2;

n is 0, 1 , 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said isosteres of carboxylic acids are selected

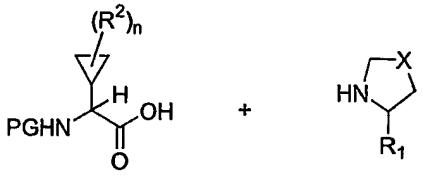
from the group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, $-COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, $-NR^3COR^4$,NR^3COOR^4, $NR^3S(O)_mR^4$, $-S(O)_mNR^3R^4$, $-OCONR^3R^4$,- OR^3 ,$-R^3$,$-SR^3$;

R^3 and R^4 may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof;

which comprises the step of:

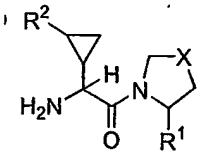
coupling of a compound of formula (III) with a compound of formula (IV):



(III) (IV)

in the presence of a coupling agent and a base in a solvent.

63. A process for the preparation of compounds of the general formula (II):



(II)

wherein:

X is selected from -S (O)$_m$, -CH_2-, CHF, and -CF_2;

m is 0, 1 or 2;

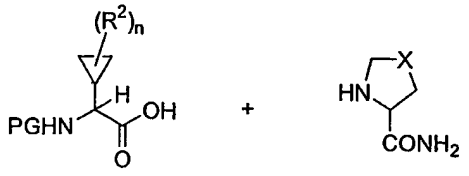
R^1 is selected from the group consisting of hydrogen, nitrile (-CN), COOH, or isosteres of carboxylic acids, wherein said isosteres of carboxylic acids are selected from group consisting of SO_3H, CONOH, $B(OH)_2$, $PO_3R^3R^4$, $SO_2NR^3R^4$, tetrazole, amides, esters and acid anhydrides;

wherein R^2 is selected from groups consisting of hydrogen, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, -$COOR^3$, CH_2OR^3, COR^3, $CONR^3R^4$, NR^3R^4 and $NR^3CONR^3R^4$, -NR^3COR^4,NR^3COOR^4, $NR^3S(O)_mR^4$, -$S(O)_mNR^3R^4$, -$OCONR^3R^4$,- OR^3 ,-R^3 ,-SR^3;

R^3 and R^4 may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl and substituted or unsubstituted carboxylic acid derivatives or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof;

which comprises the step of:

coupling of a compound of formula (III) with a compound of formula (IVA):



(III) (IVA)

in the presence of a coupling agent and a base in a solvent.

64. The process according to claim 60 or 61, wherein said coupling is performed from about 3 to about 48 hours.

65. The process of claims 60 or 61, wherein said coupling agent is selected from the group consisting of EDC, HOBt and DCC.

66. The process of claims 60 or 61, wherein said base is selected from the group consisting of diisopropylethylamine and triethylamine.

67. The process of claim 60 or 61, wherein said solvent is selected from the group consisting of DMF and methylene chloride.

INTERNATIONAL SEARCH REPORT

PCT/IB2004/004148

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/04 C07D207/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/002531 A (SMITHKLINE BEECHAM CORPORATION; HAFFNER, CURT, DALE; MCDOUGALD, DARRYL) 9 January 2003 (2003-01-09) page 1, paragraph 1 example 21 claim 33	1,55
A	EP 1 258 476 A (LES LABORATOIRES SERVIER) 20 November 2002 (2002-11-20) page 1, paragraph 1 claim 2	1,55

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2005	29/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/004148

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 57-59
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57-59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IB2004/004148

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002531 A	09-01-2003	BR 0210644 A	20-07-2004
		CA 2450722 A1	09-01-2003
		CZ 20033521 A3	12-05-2004
		EP 1399433 A2	24-03-2004
		EP 1399420 A2	24-03-2004
		EP 1406873 A2	14-04-2004
		HU 0400321 A2	30-08-2004
		JP 2004535445 T	25-11-2004
		JP 2005500321 T	06-01-2005
		MX PA03011907 A	26-03-2004
		WO 03002530 A2	09-01-2003
		WO 03002553 A2	09-01-2003
		WO 03002531 A2	09-01-2003
		US 2004167341 A1	26-08-2004
		US 2004171848 A1	02-09-2004
		US 2004242636 A1	02-12-2004
EP 1258476 A	20-11-2002	FR 2824825 A1	22-11-2002
		AU 4065402 A	21-11-2002
		BR 0201697 A	06-05-2003
		CA 2383298 A1	15-11-2002
		CN 1385421 A ,C	18-12-2002
		EA 4865 B1	26-08-2004
		EP 1258476 A1	20-11-2002
		HU 0201646 A2	28-02-2003
		JP 2002363157 A	18-12-2002
		NO 20022285 A	18-11-2002
		NZ 518948 A	31-10-2003
		PL 353910 A1	18-11-2002
		US 2003078247 A1	24-04-2003
		ZA 200203867 A	02-01-2003